

Diastereoselective Lithiation-Substitution of *N*-Silyl-Protected-(*S*)-Tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-3(2*H*)-ones and Applications of Their Derivatives

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Abstract

This thesis describes a method involving the preparation of an *L*-proline-derived imidazolone protected with an *N*-triethylsilyl group that undergoes diastereoselective lithiation followed by electrophile quench to give C5-substituted products with *syn* stereochemistry. The *N*-silylated derivatives may be more easily *N*-deprotected as compared to previous *N*-*t*-Bu analogues to give secondary ureas. These may serve as precursors to *N*-phenyl chiral bicyclic guanidines or as NHC precursors for synthesis of corresponding complexes.

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¹ H & ¹³ C NMR of 161	95
¹ H & ¹³ C NMR of 162	96
¹ H & ¹³ C NMR of 181	97
¹ H & ¹³ C NMR of 182	98
¹ H & ¹³ C NMR of 183	99
¹ H & ¹³ C NMR of 184	100
¹ H & ¹³ C NMR of 185	101
¹ H & ¹³ C NMR of 186	102
¹ H & ¹³ C NMR of 187	103
¹ H & ¹³ C NMR of 188	104
¹ H & ¹³ C NMR of 189	105
¹ H & ¹³ C NMR of 190	106
¹ H & ¹³ C NMR of 174	107
¹ H & ¹³ C NMR of 175	108
¹ H & ¹³ C NMR of 191	109
¹ H & ¹³ C NMR of 166	110
¹ H & ¹³ C NMR of 194	111
¹ H & ¹³ C NMR of 195	112
¹ H & ¹³ C NMR of 196	113
¹ H & ¹³ C NMR of 197	114
¹ H & ¹³ C NMR of 199	115
¹ H & ¹³ C NMR of 202	116
¹ H & ¹³ C NMR of 205	117
¹ H & ¹³ C NMR of 206	118
¹ H & ¹³ C NMR of 207	119
¹ H & ¹³ C NMR of 203	120
¹ H & ¹³ C NMR of 204	121
¹ H & ¹³ C NMR of 167	122
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¹ H & ¹³ C NMR of 240	124
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HPLC for **220c** and **220a**
HPLC for **220b**

141
142

Abbreviations

Ac	acetyl
Ar	aryl
adm	adamant-1-ylbroad
b	broad
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
B ₂ (pin) ₂	bis(pinacolato)diboron
Bu	butyl
cat	catalyst
Cbz	carbobenzyloxy
CHDA	1,4-diaminocyclohexane
COD	1,5-cyclooctadiene
COSY	correlation spectroscopy
d	doublet
dba	dibenzylidene acetone
DBU	1,5-diazabicyclo[4.3.0]non-5-ene
De	diastereomeric excess
DMC	2-chloro-1,3-dimethylimidazolinium chloride
DMCHDA	dimethylcyclohexane-1,2-diamine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
ee	enantiomeric excess
El	electron impact
ELMS	electron impact mass spectrum
Equiv	equivalents
er	enantiomeric ratio
EWG	electron withdrawing group
FAB	fast-atom bombardment
h	hours
HOBt	hydroxybenzotriazole
HRMS	high resolution mass spectrum
KHMDS	potassium hexamethyldisilazan
KOt-Bu	potassium <i>tert</i> -butoxide
IR	infrared
LiAlH ₄	lithium aluminum hydride
m	multiplet
mes	mesityl
MVK	methyl vinyl ketone
mp	melting point
MTBE	methyl <i>tert</i> -butyl ether
NBS	<i>N</i> -bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMR	nuclear magnetic resonance
HSQC	heteronuclear single quantum coherence
NOE	nuclear Overhauser enhancement
NOESY	nuclear Overhauser enhancement spectroscopy
OAc	acetoxy
Ph	phenyl
pin	pinacolate
POCl ₃	phosphoryl chloride
q	quartet
<i>rac</i>	racemic

rt	room temperature
s	singlet
t	triplet
TC	thiophene-2-carboxylate
TES	triethylsilane
THF	tetrahydrofuran
TMS	trimethylsilyl
Tr	Trityl (triphenylmethyl)
t _R	retention time

1. Introduction

Saturated cyclic amines are a common structural motif in natural products and biologically active compounds, and an important template for versatile catalysts for a wide range of organic transformations. Piperidine and pyrrolidine heterocyclic amines occur widely in nature as constituents of quinolizidine, pyrrolizidine and indolizidine alkaloids, which exhibit interesting and diverse biochemical, pharmaceutical and agricultural properties as a result of their diverse biological activities.¹ Prominent examples of these systems are natural compounds such as nicotine and coniine, anisomycin, oxiracetam, plakoridine, as well as the opiates codeine and morphine (**Figure 1**).

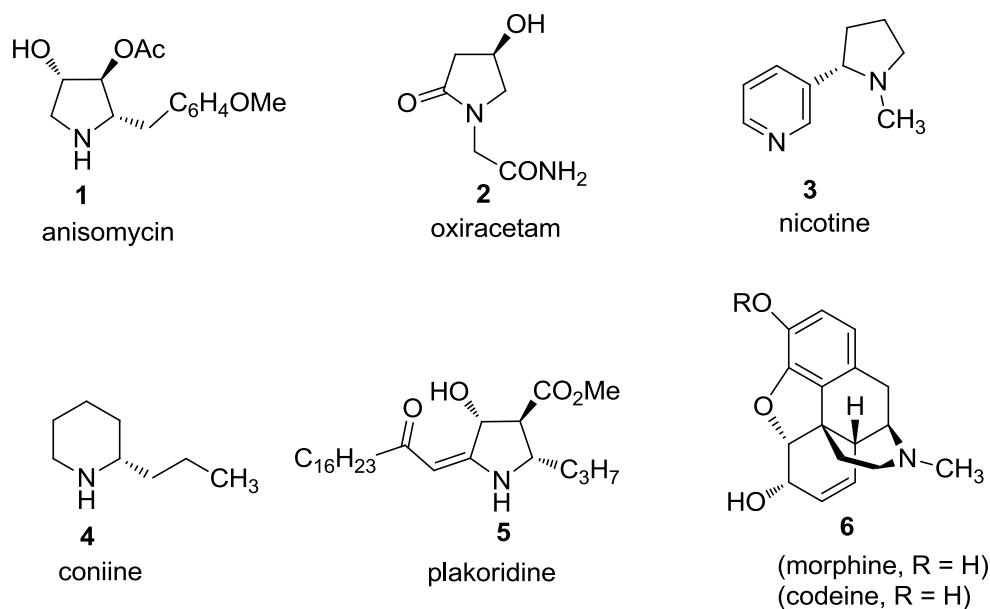


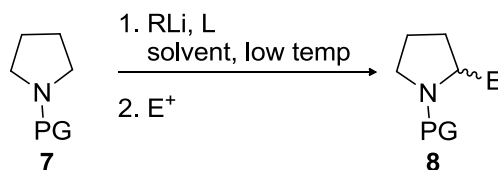
Figure 1. Some biologically active nitrogen-containing heterocycles.¹

Achiral and chiral pyrrolidine heterocyclic amines are important structural motifs in potential catalysts for asymmetric synthetic chemistry and in natural products. Asymmetric lithiation is the most powerful synthetic method for synthesis of chiral pyrrolidine derivatives.²

1.1. Direct α -Functionalization of Saturated Cyclic Amines

The direct functionalization of nitrogen-containing heterocycles has recently become an important route in organic synthesis.² This is achieved with saturated cyclic amines by the addition of a protecting group to the nitrogen, α -lithiation, electrophilic substitution, and finally, deprotection of nitrogen.³ In fact, this straightforward way for direct α -functionalization of the saturated cyclic amines³ has great utility in the alkaloid synthesis of potential pharmaceuticals and natural product synthesis.⁴ Thus, this method may lead to further development of related compounds as potential medicinal agents.

The direct functionalization of nitrogen-containing heterocycles can be derived by α -lithiation by alkyllithium and appropriate diamine complexes, production of active carbanion, followed by electrophilic substitution.³ Several protecting groups, including carbamates, formadines, oxazolines, amides and phosphoramides, were effective in α -functionalization of the nitrogen containing-heterocycles, which were reported by Beak and Hoppe (**Scheme 1**).^{5a,b}



R = *s*-Bu, *n*-Bu, *i*-Pr

PG = Boc, Et, *n*-Bu, *i*-Bu, CH₂CH₂OMe

trimethylallyl, 3-methylbut-2-enyl

Scheme 1. Asymmetric deprotonation of *N*-protected pyrrolidines with chiral diamine and alkyllithium^{4,5}

O'Brien and co-workers have reported the asymmetric deprotonation of pyrrolidine by the use of (–)-sparteine as a chiral diamine, which allows for removal of one of the pro-*S* protons. They also used other diamine ligands such as TMEDA, PMDETA as well as the (+)-sparteine surrogate, which have caused significant development in the α -lithiation strategy and provided a synthetic route to access both enantiomeric forms of α -substituted pyrrolidine derivatives (**Figure 2**).⁶

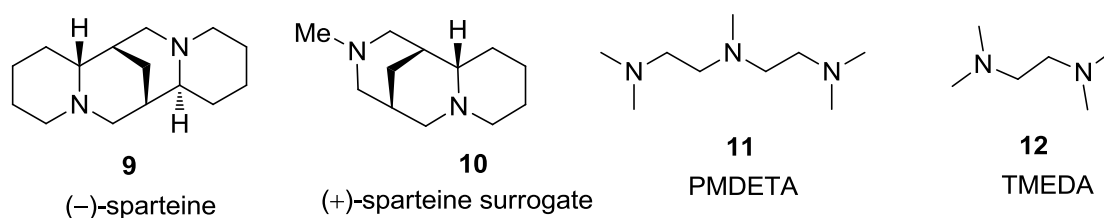
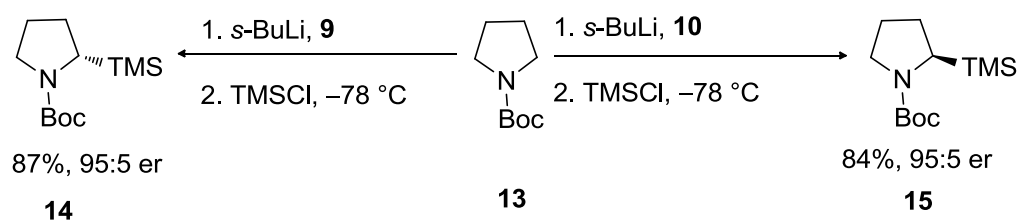
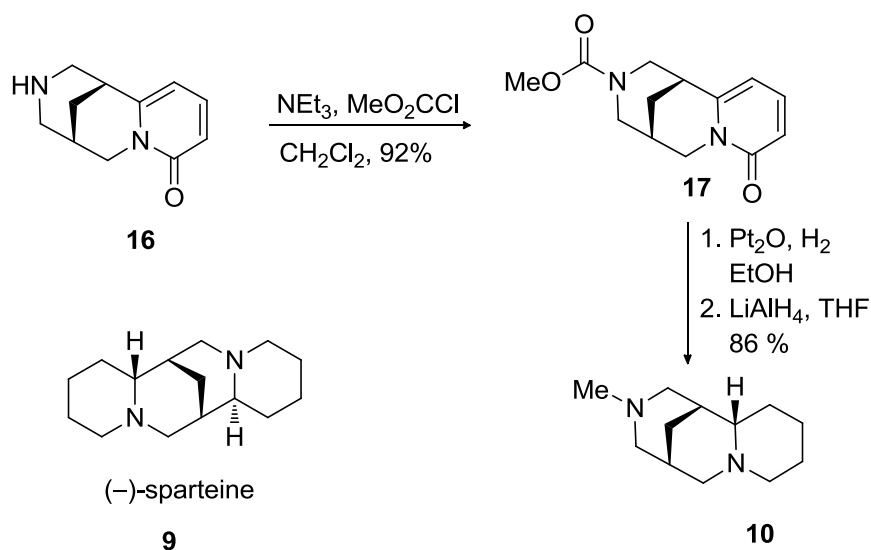


Figure 2. Structures (–)-sparteine **9** and (+)-sparteine surrogate **10**, PMDETA and TMEDA.⁶

They have highlighted the importance and effectiveness of both (+)-surrogate and (–)-sparteine in the asymmetric deprotonation with the opposite sense of enantioselectivity (**Scheme 2**). (+)-Surrogate **10** was generated from cytosine **16** in excellent yield (**Scheme 3**).⁷



Scheme 2. Influence of both (+)-sparteine surrogate and (–)-sparteine in asymmetric deprotonation.⁷



Scheme 3. Synthesis of (+)-sparteine surrogate **10**.⁷

Pre-complexation of nitrogen with borane or boron trifluoride for the activation of tertiary amines to regioselective lithiation-substitution reactions play important role as a valuable method in organic synthesis.⁸ The most of studies in this area have focused on lithiation of sp^3 -hybridized carbon atoms alpha to nitrogen in cyclic amines such as Troeger's base **18**,⁹ isoindolines **19**,^{10a,b} pyrrolidines **20**¹¹ and indolizidines **21**,¹² For these substrates **19** and **20**, lithiation of prochiral α -methylene groups with alkylolithiums in the presence of the chiral diamine (-)-sparteine after electrophile quench gave enantiomerically enriched products. For example, (-)-sparteine-mediated lithiation-substitution of isoindolines gave products ranging from 78:22–94:6 er via intermediate **19**. Under the same conditions, enantiomerically enriched carbanion **20** was generated in 85:15–86:14 er, determined as the benzophenone adducts (28–78% yield) (**Figure 3**).

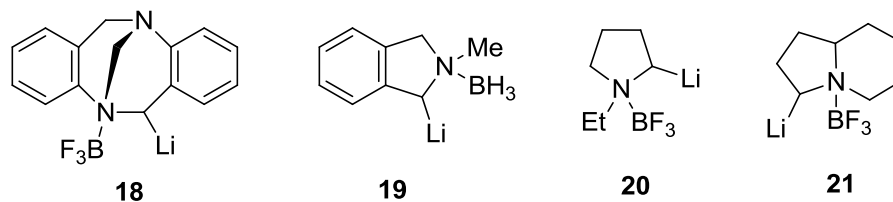
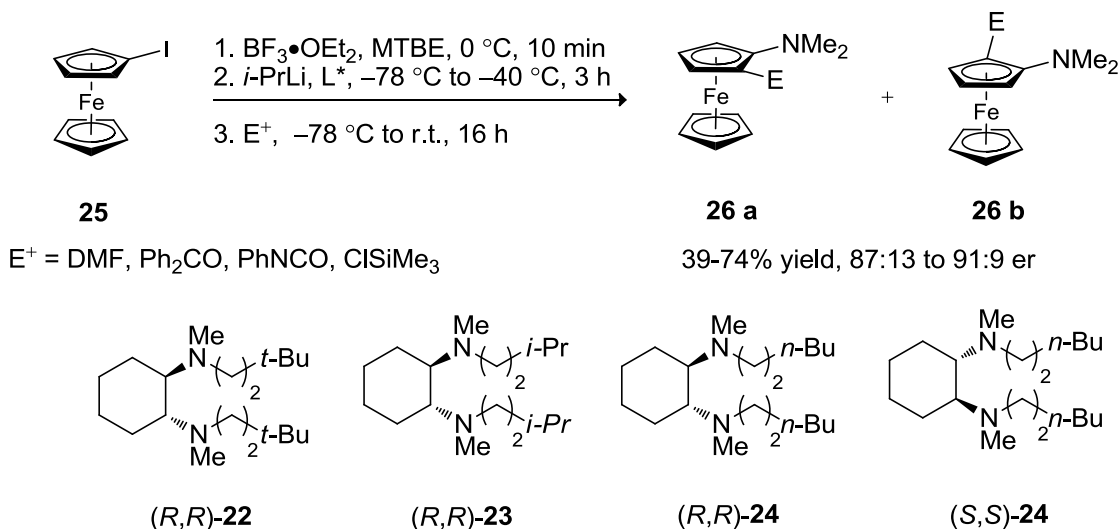


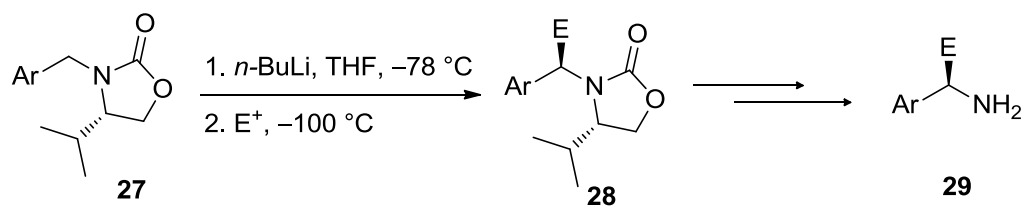
Figure 3. Previous examples of BF_3 - or BH_3 -activated lithiation of tertiary amines.

Metallinos and co-workers reported the first example of BF_3 -activated asymmetric lithiation of an sp^2 -hybridized carbon atom of a prochiral aromatic amine, and the first application of bulky chiral 1,2-diaminocyclohexane ligands such as **22-24** in the BF_3 -activated tertiary aminoferrocenes, rather than (–)-sparteine. The process provided access to a broad range of enantiomerically enriched 2-substituted-1-aminoferrocenes in high enantioselectivity (87:13 to 91:9 er) after simple recrystallization (**scheme 4**).¹³



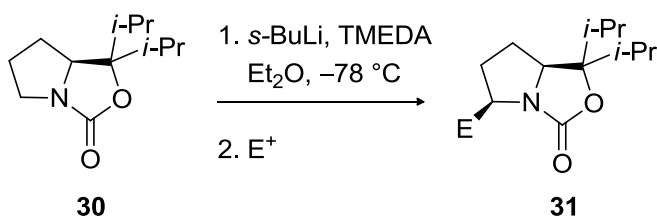
Scheme 4. Asymmetric lithiation of boron trifluoride-activated amino-ferrocenes.

Recently, this method has become more versatile by the development of (+)-sparteine surrogate **10** and it is also now possible to install vinyl and aryl substituents with retention of stereochemical integrity of the chiral carbanion.¹⁴ The first synthesis of chiral benzylamines **29** from oxazolidones via diastereoselective lithiation was reported by Gawley and co-workers with good yields and excellent diastereoselectivities (**Scheme 5**).¹⁵



Scheme 5. Diastereoselective synthesis of chiral benzylamines from oxazolidones.¹⁰

Following diastereoselective lithiation procedure, Beak examined competition experiments between a series of *N*-Boc amines and bicyclic carbamates. The results indicated that rigid carbamates were deprotonated faster than *N*-Boc amines. Beak determined that these reactions undergo diastereoselective lithiation in the presence of a chiral centre in the substrate to give products **31** with *syn* stereochemistry (**Scheme 6**).¹⁶



Scheme 6. Diastereoselective lithiation of bicyclic carbamate **31**.¹¹

It was indicated that removal of one of the pro-*S* protons is favoured and the resulting anion is configurationally stable. These results proposed that appropriate restriction of the geometry of the substrate can increase the ability of the lithiation reaction and a small dihedral angle between the carbonyl group and the proton that is being removed is favoured.

The distance between the carbamate carbonyl group and the proton removed was calculated at the PM3 level.¹¹ These computational calculations showed that the pro-*R* proton had a much longer distance to the carbonyl oxygen (3.70 Å) than the pro-*S* proton (2.78 Å). Removal of the pro-*S* proton which is nearest proton to the carbonyl oxygen is kinetically, as well as thermodynamically favored (**Figure 4**).

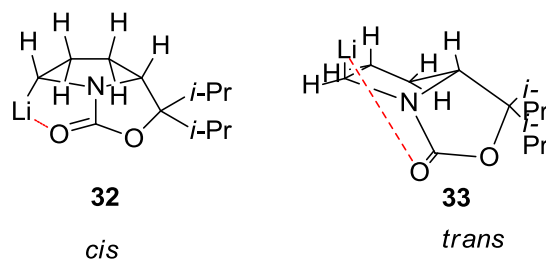
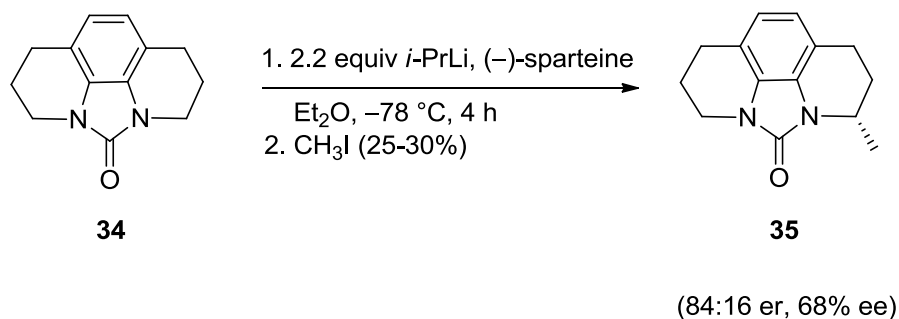


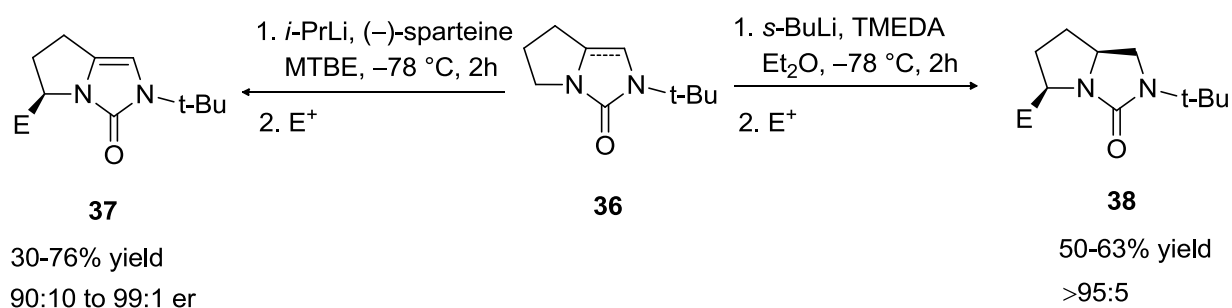
Figure 4. Geometry between the lithium and the carbonyl group in *cis* and *trans* carbanions.¹¹

Following a similar procedure, Metallinos and co-workers reported in 2007¹⁷ asymmetric lithiation alpha to nitrogen of urea-fused piperidines by using *i*-PrLi (–)-sparteine. According to the procedure described for bicyclic carbamates, an octahydrophenanthroline-derived urea **34** was lithiated by *i*-PrLi followed by electrophile quench to generate **35** in low yield and moderate enantioselectivities (**Scheme 7**). The transition state analysis for the lithiation of urea **34** by the *i*-PrLi and (–)-sparteine complex was performed at the MP2/G-31G(d)//B3LYP/6-316(d) level of theory, and showed that the removal of the axial pro-*R* hydrogen is less favoured than equatorial pro-*S* hydrogen.¹²



Scheme 7. Lithiation of octahydrophenanthroline-derived urea **34**.¹²

Notably, they reported a new method to access enantiomerically enriched products of both pyrrolo[1,2-c]imidazolin-3-ones and pyrrolo[1,2-c]imidazol-3-ones, which are relatively challenging and problematic to make by conventional ways. They showed that 5-substituted pyrroloimidazolium and pyrroloimidazolinium precatalysts can be prepared in two steps by stereoselective lithiation followed by electrophilic quench of their lithio derivatives (**Scheme 8**).¹⁸



Scheme 8. Synthesis of saturated and unsaturated ureas by stereoselective lithiation.¹³

The next section will briefly introduce pyrrolidine-containing molecules which are used as catalysts in organic reactions.

1.2. Guanidines

Guanidines (**Figure 5**) are present in many natural products, which are often found to have significant biological activities¹⁹ as well their potential as substrate specific oxoanion hosts.²⁰ Guanidines are obtained by the oxidation of guanine, synthesized for the first time by oxidative degradation of an aromatic natural product in 1861.²¹

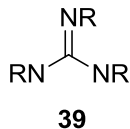


Figure 5. General structure of guanidines.

A large number of guanidines consist of marine guanidines, which are found as anionic receptors that can react with phosphates and carboxylates due to hydrogen bonding.¹⁵

Guanidines are classified as organic superbases and catalyze a variety of base-assisted organic transformations due to the resonance stability of their conjugate acids. The guanidine compound, 1,1,3,3-tetramethylguanidine (or *N,N,N',N'*-tetramethylguanidine; TMG) **40** has been used in a wide range of organic transformations as its substituted ones **41** used by Barton (**Figure 6**).²²

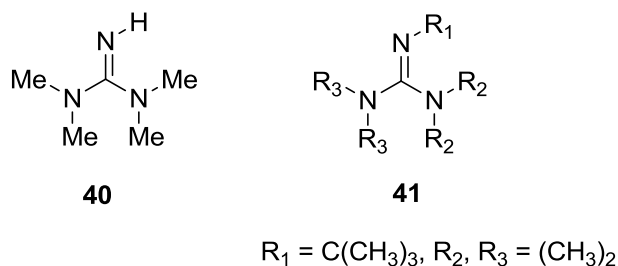
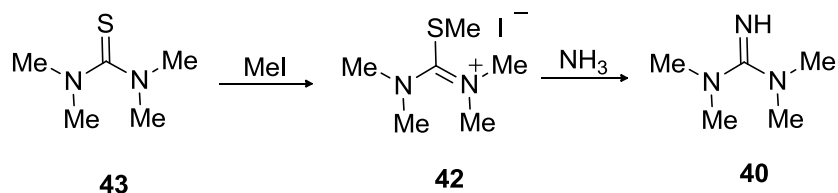


Figure 6. Structures of TMG **40** and Barton's bases **41**.¹⁷

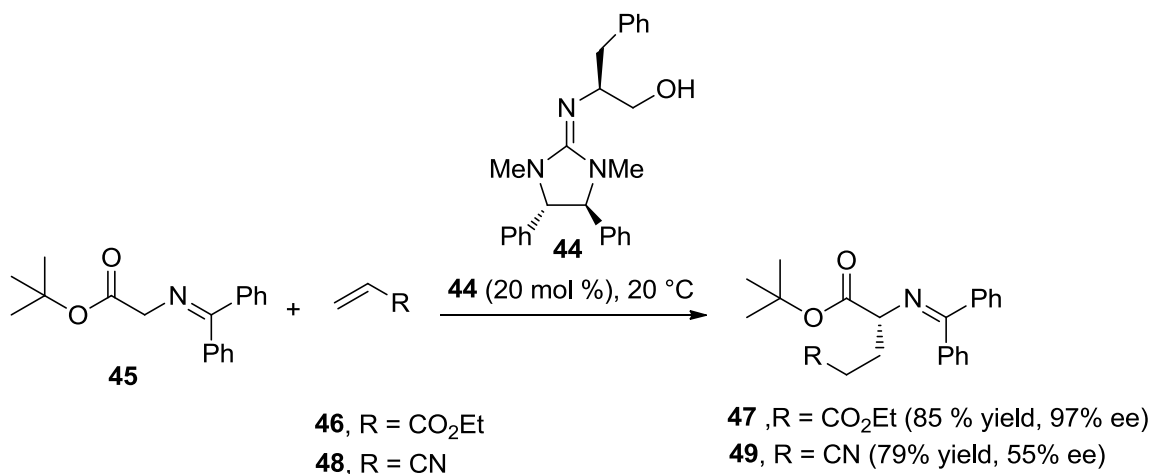
1.2.1. Synthesis of Polysubstituted Acyclic and Monocyclic Guanidines and Their Applications

TMG was synthesized for the first time by Schneck by treatment of 1,1,3,3-tetramethyl-2-methylthioamminium salt and ammonia in 1912 (**Scheme 9**).²³



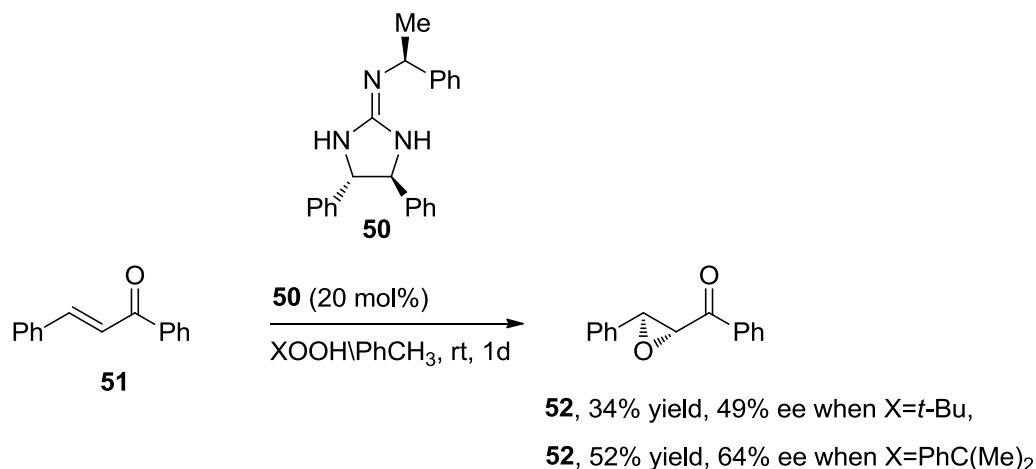
Scheme 9. Synthesis of guanidine **41** by Schenck.¹⁸

As an application of monocyclic guanidines, guanidine **44** was used by Ishikawa and co-workers to catalyze the Michael reaction of glycinate under solvent-free conditions, in which they obtained a high yield of 85% and good enantiomeric excess (ee). However, **48** only gave **49** in 79% yield and 55% ee, and required 3-5 days to reach completion (**Scheme 10**).²⁴



Scheme 10. Application of monocyclic guanidines in Michael reaction of glycinate.¹⁹

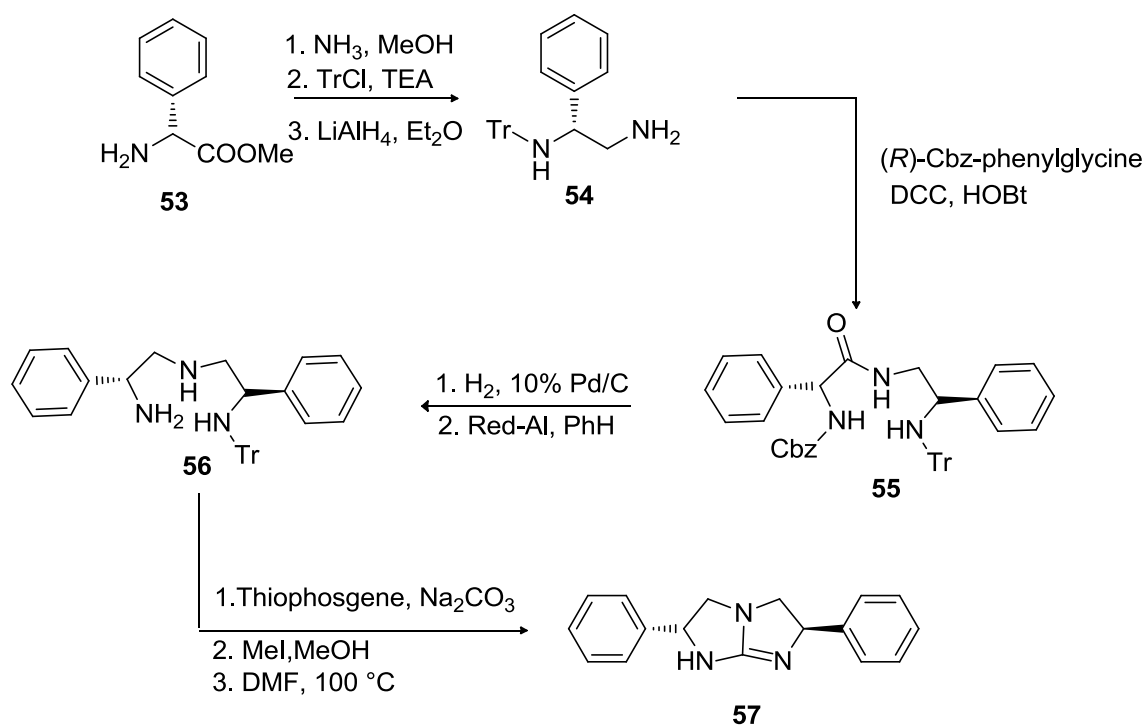
The hydroxyl group in the catalyst **44** was crucial for asymmetric induction in this process. Further attempts to optimize asymmetric induction were done by Ishikawa by using another monocyclic guanidine **50** in the asymmetric epoxidation of chalcone with different hydroperoxides. The result indicated epoxides **52** in 49% and 64% ees (**Scheme 11**).²⁵



Scheme 11. Epoxidation of chalcone catalyzed by monocyclic guanidine **50**.²⁰

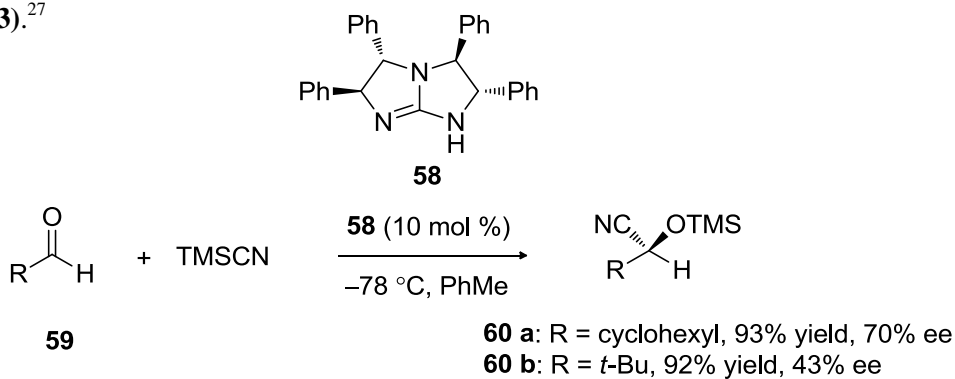
1.2.2. Synthesis of Bicyclic Guanidines and Their Applications

Corey and Grogen synthesized *pseudo* C₂-symmetric bicyclic guanidines for the first time from (*R*)-phenylglycine and used it as a symmetrical bicyclic guanidine catalyst in a Strecker reaction in 1999 (**Scheme 12**).²⁶ A trityl-protected diamine was obtained by reacting methyl (*R*)-phenylglycinate with ammonia-saturated methanol to afford the desired amide. Subsequent to reduction of **53** by lithium aluminum hydride in ether, and coupling of **54** to CBz protected phenylglycine yielded amide **55**. Conversion to triamine **56** was completed by carbamate hydrogenolysis, and reduction with sodium bis (2-methoxyethoxy) aluminum dihydride. Thiourea was generated by treatment of **56** with thiophosgene and aqueous sodium carbonate. After methylation with iodomethane, the desired guanidine **57** was obtained in a 55% yield after heating in DMF at 100 °C.



Scheme 12. Synthesis of *pseudo* C_2 -symmetric bicyclic guanidine **57**.²¹

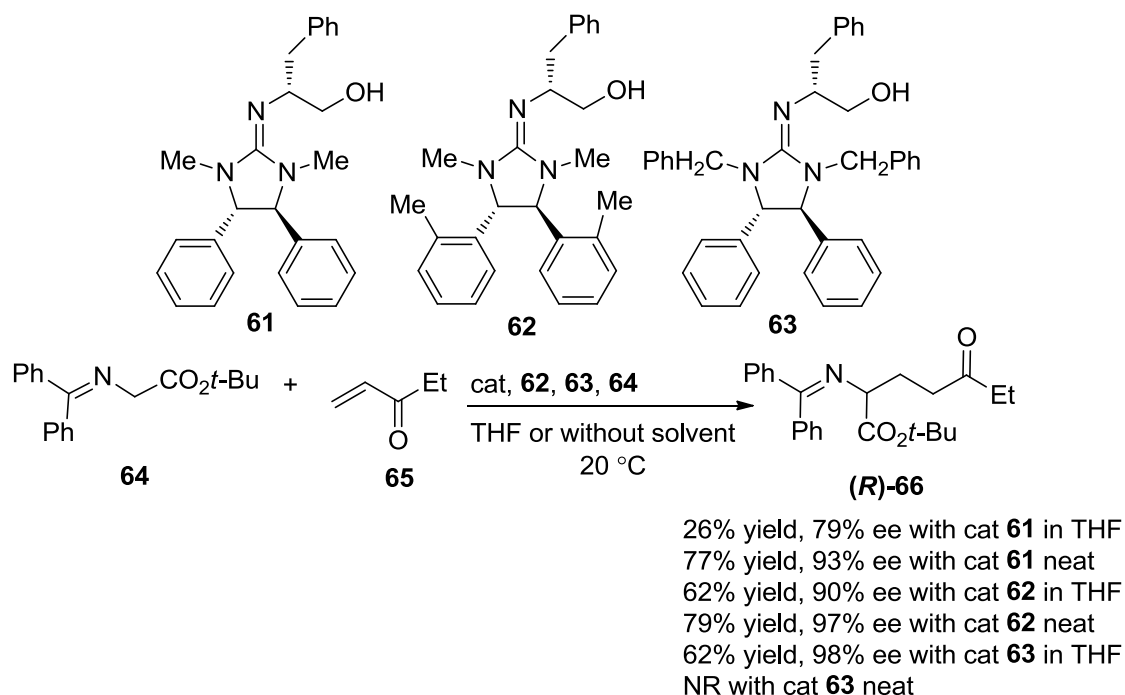
Ishikawa and co-workers used *pseudo* C_2 -symmetric bicyclic guanidine **58** in the TMS cyanation of aliphatic aldehydes and ketones, obtaining the products **60a,b** with moderate enantiomeric excess (**Scheme 13**).²⁷



Scheme 13. Cyanation of aliphatic aldehydes and ketones catalyzed by *pseudo* C_2 -symmetric guanidine

58.²²

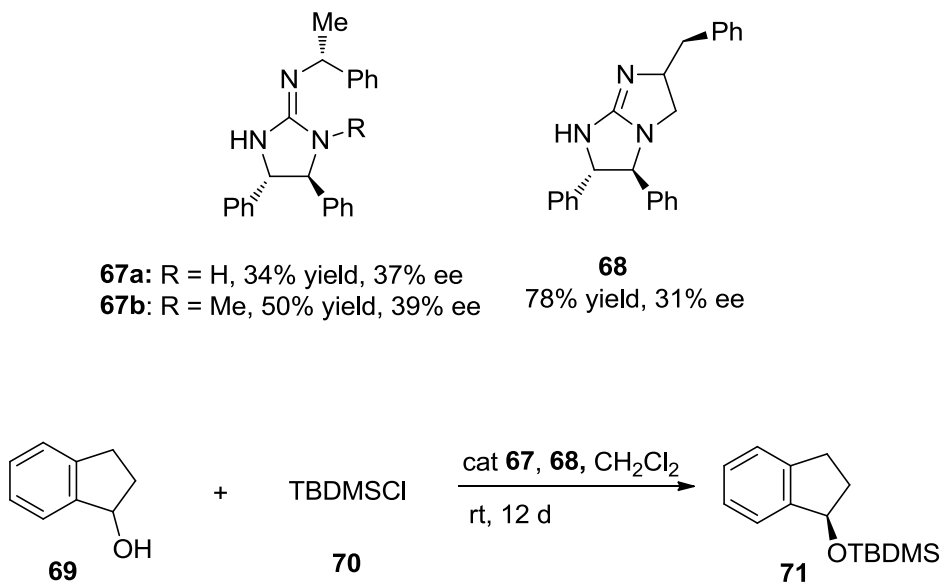
In a following attempt, they applied the 1,3-dimethyl-4,5-bis(2-methylphenyl) imidazolidine and the related 1,3-dibenzyl-4,5-diphenylimidazolidine in the asymmetric Michael reaction of *t*-butyl diphenyliminoacetate and ethyl acrylate. The results showed good selectivity (79-98% ee). Also they found that selectivity and activity can be improved by installing the methyl group on the *ortho* position of the phenyl pendant in 1,3-dimethyl-4,5-bis(2-methylphenyl) imidazolidine and the related 1,3-dibenzyl-4,5-diphenylimidazolidine (**Scheme 14**).²⁸



Scheme 14. Asymmetric Michael reaction of *t*-butyl diphenyliminoacetate and ethyl acrylate catalyzed by guanidines **61**, **62**, **63**.²³

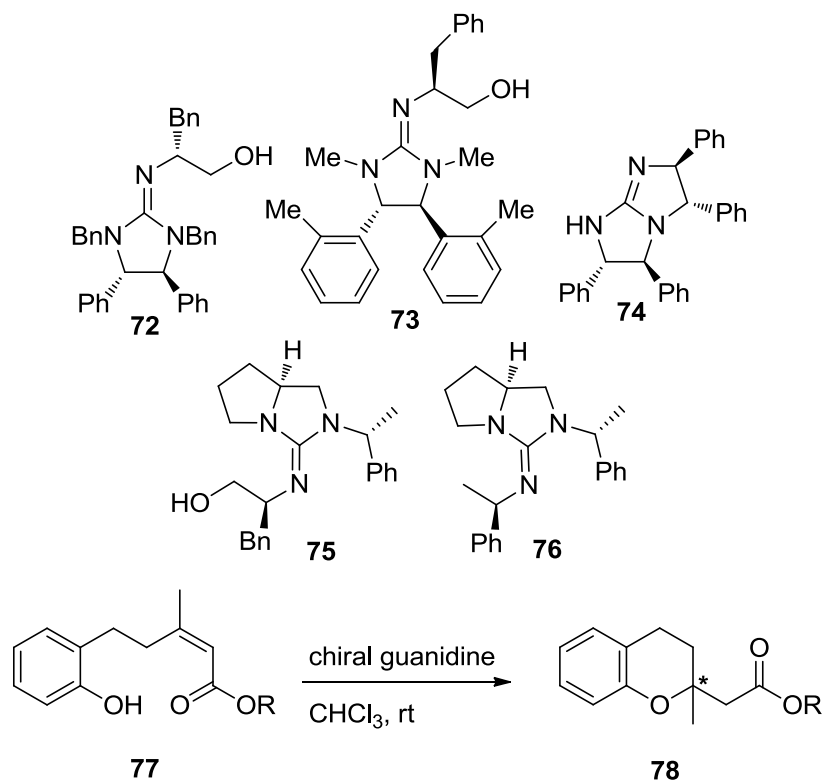
Kinetic resolution of *sec*-alcohols by silylation catalyzed by a variety of modified guanidines did not provide good selectivity, among them only **67a**, **67b** and **68** gave moderate enantioselectivity (31-50% ee).²⁹ Ishikawa and co-workers improved selectivity when they used a bulkier triisopropylsilyl

chloride as a silylating agent (70% ee) as compared to *tert*-butyldimethylsilyl chloride (TBDMSCl) in reaction of indanol **69** (Scheme 15).



Scheme 15. Reaction of indanol **68** with *tert*-butyldimethylsilyl chloride catalyzed by **67a**, **67b** and **68**.²⁴

Quaternary carbon stereocentres are found in a wide range of organic compounds, including important medicinal agents and bioactive natural products. A variety of modified guanidines were examined in construction of quaternary carbon centres in the chromane skeleton by intramolecular oxa-Michael addition.³⁰ Good asymmetric induction was observed when *Z* unsaturated esters were used as the substrates in reactions catalyzed by (4*S*,5*S*)-2-[(*R*)-1-hydroxymethyl-2-phenylethylimino]-1,3-dimethylimidazolidine **73** (Scheme 16).



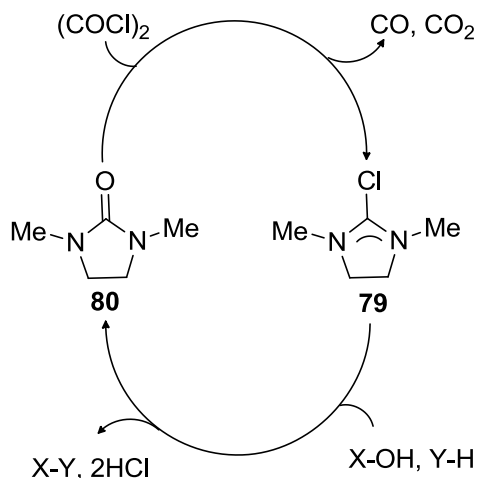
R = Me, Et

cat **72**, R = Me, 39% yield, 23% ee
 cat **73**, R = Me, 41% yield, 80% ee
 cat **74**, R = Et, NR
 cat **75**, R = Et, 10% yield, 2% ee
 cat **76**, R = Et, 39% yield, 1% ee

Scheme 16. Construction of quaternary carbon centre by intramolecular oxa-Michael addition catalyzed by guanidines **72-76**.²⁵

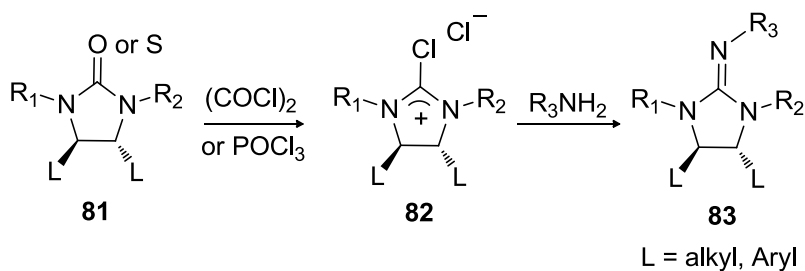
1.2.3. DMC Chemistry

Chloroamidinium salts such as 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and *N,N,N',N'*-tetramethylchloroformamidinium chloride are strong dehydration agents, and can chlorinate alcohols and reduce sulfoxides.³¹ DMC is stable toward moisture and oxygen. Chloroamidinium salts have two advantages: 1) the easy removal of the excess starting material and regenerated salt by work-up, and 2) straightforward preparation (**Scheme 17**). DMC **79** is generated by reaction of **80** with phosphoryl chloride, oxalyl chloride or trichloromethyl chloroformate.

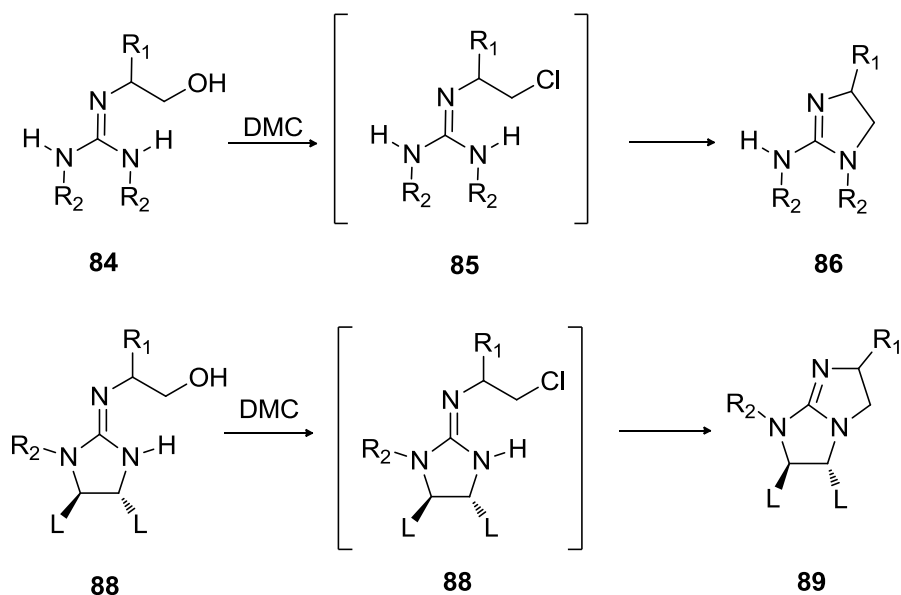


Scheme 17. Conversion of DMI to DMC and vice versa.

Guanidines can be synthesized by reaction of DMC with the appropriate amines. Thus DMC chemistry has developed into a methodology for obtaining both mono and bicyclic guanidines. **Scheme 18a** shows the synthesis of trisubstituted monocyclic guanidines via the reaction of DMC-type chloroamidine compounds with amines. **Scheme 18b** shows cyclization of guanidines by DMC chemistry.^{32a,b}



Scheme 18a. Synthesis guanidines via reaction of DMC-type chloroamidine compounds.^{27a}

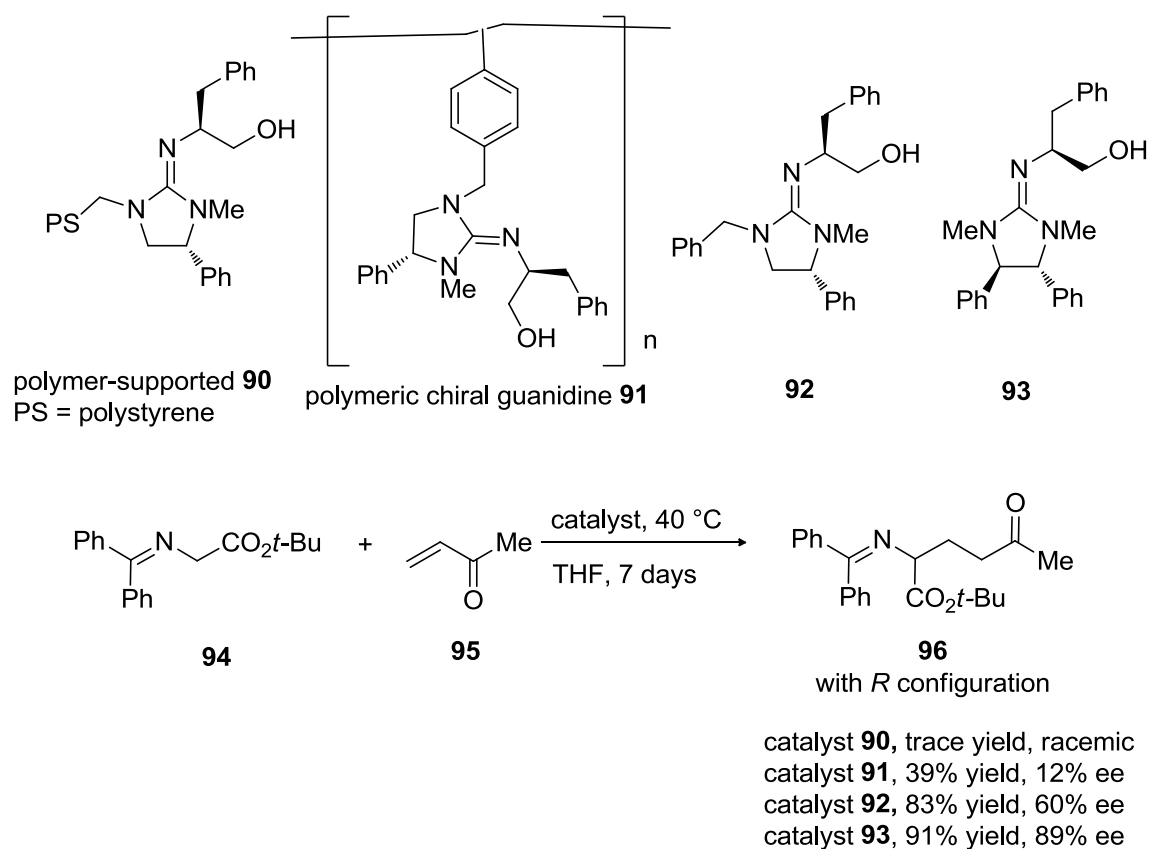


Scheme 18b. Cyclization of guanidines by DMC chemistry.^{27b}

1.2.4. Guanidines as Synthetic Tools

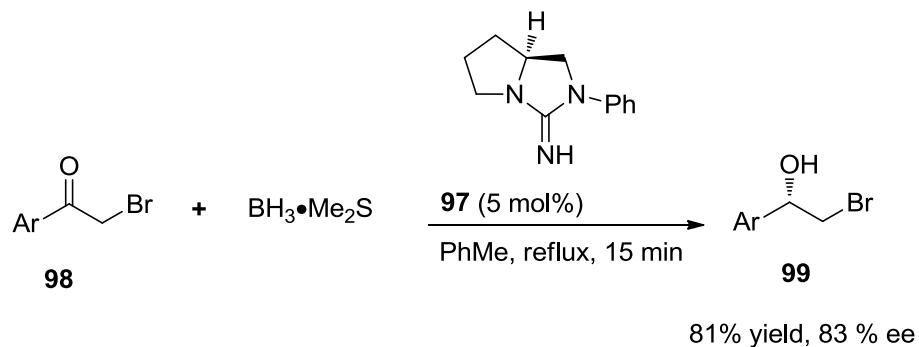
Chiral guanidines have been used as potential catalysts in numerous asymmetric transformations. Ishikawa, in 2005, designed several polymer-based chiral guanidines and used them in the asymmetric Michael reaction of *t*-butyl diphenyliminoacetate with MVK (**Scheme 19**).³³

The turnover was observed to range from low to good enantioselectivity. In the case of polymer-supported guanidine **90**, no selectivity was observed. This might be caused by the steric hindrance around the active site due to the polystyrene group directly attached to the guanidine. A Michael reaction in the presence of catalyst guanidines **92** and **93** afforded moderate selectivity. (**Scheme 19**).



Scheme 19. The turnover of the polymer-based chiral guanidines in asymmetric Michael reaction of *t*-butyl diphenyliminoacetate with MVK **95**.²⁸

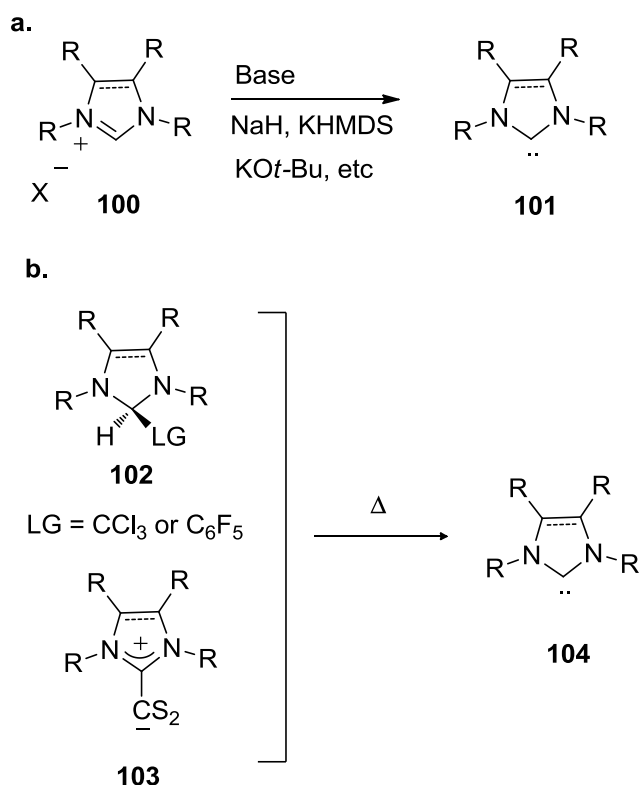
The development of active chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones has attracted much attention due to the applications of homochiral secondary alcohols in organic and medicinal chemistry. Basavaiah and co-workers applied guanidine **97** in the borane-mediated reduction of phenacyl bromide (**Scheme 20**).³⁴ They reported that higher enantioselectivity values were achieved when the reaction was done in reflux conditions as compared to room temperature.



Scheme 20. Reduction of phenacyl bromide catalyzed by guanidine **97**.²⁹

1.3. NHC Carbenes

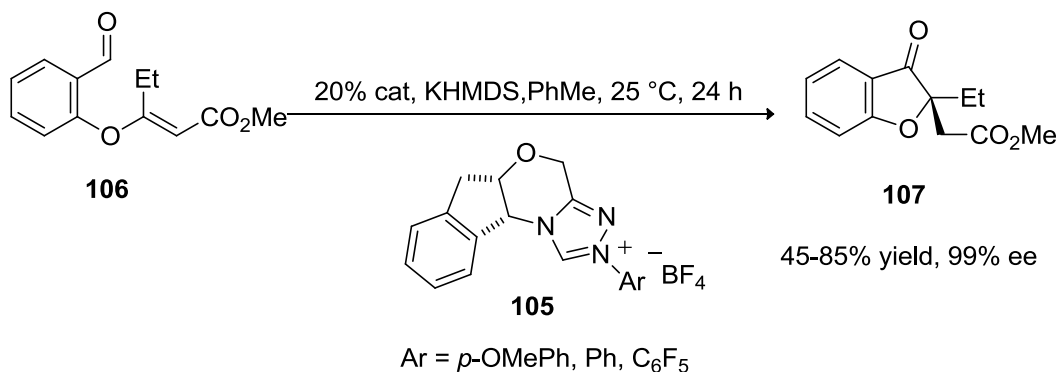
Carbenes are classified as Lewis bases, which act as excellent σ -donors and poor π -acceptors. Although they are often less economical and environmentally friendly than other metal-free catalysts, *N*-heterocyclic carbenes (NHCs) belong to the family of nucleophilic carbenes, which are known as organocatalysts and are considered as excellent ligands for metal-based catalysis.³⁵ Most heterocyclic carbenes are stable and can be isolated. Deprotonation of imidazolium or imidazolinium salts with a strong base such as sodium hydride, potassium hexamethyldisilazane, (KHMDs) or potassium *tert*-butoxide (KO*t*-Bu) (**Scheme 21a**). This approach was used by Arduengo in the original isolation of a free carbene.³⁶ Alternatively, the desired carbene species can be thermodynamically generated from the related 2-trichloromethyl, 2-pentafluorophenyl, 2-carboxylated, or 2-dithiocarboxylated “protected” NHC adducts (**Scheme 21b**).^{37a,b}



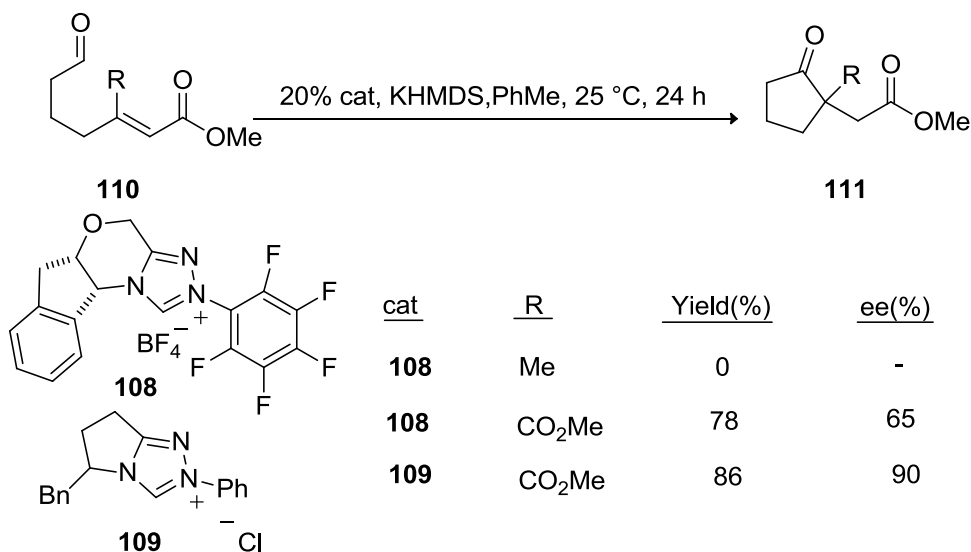
Scheme 21a,b. Generation of free NHC carbene ligands by two methods.^{31,32ab}

1.3.1. Application of *N*-Heterocyclic Carbenes in Asymmetric Organic Reaction

N-Heterocyclic carbenes (NHCs) can act as effective nucleophilic catalysts in organic reactions. Rovis reported synthesis of quaternary stereocenters by using triazolium catalysts.³⁸ The 1,4-dicarbonyl compounds were generated in high yield and enantioselectivity under mild conditions. Moreover, the effect of a series of the aminoindanol-derived catalysts **105** in construction of the quaternary stereocentre of compound **107** determined that in all cases tertiary ether **107** was generated in excellent enantioselectivity (**Scheme 22**). Attempt to the synthesis of the 1,4-dicarbonyl compounds using the less activated olefin (R = Me) in methyl ester **110** failed, but compound **110** with CO₂Me group gave bis-methyl ester **111** in 78% yield and 65% ee (**Scheme 23**).

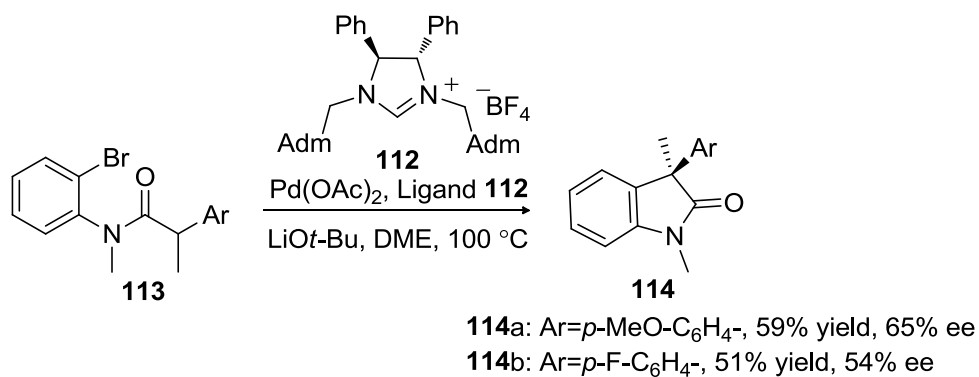


Scheme 22. Synthesis of quaternary stereocenters by using triazolium catalysts.³³



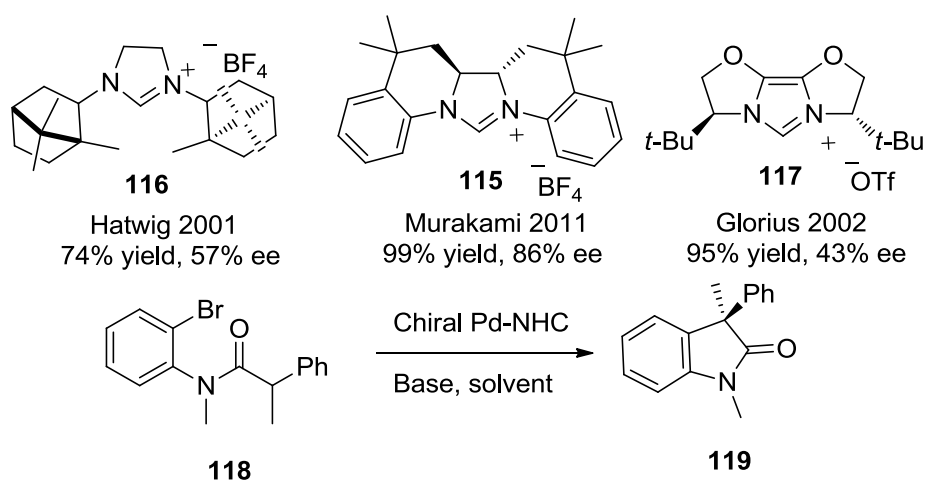
Scheme 23. Cyclization of bis-methyl ester catalyzed by **108** and **109**.³³

Aoyama designed a new class of *N*-heterocyclic carbene ligands for asymmetric catalysis in the Pd-catalyzed intramolecular α -arylation of anilides for generation of 3,3-disubstituted oxindoles with moderate enantioselectivity (**Scheme 24**).³⁹



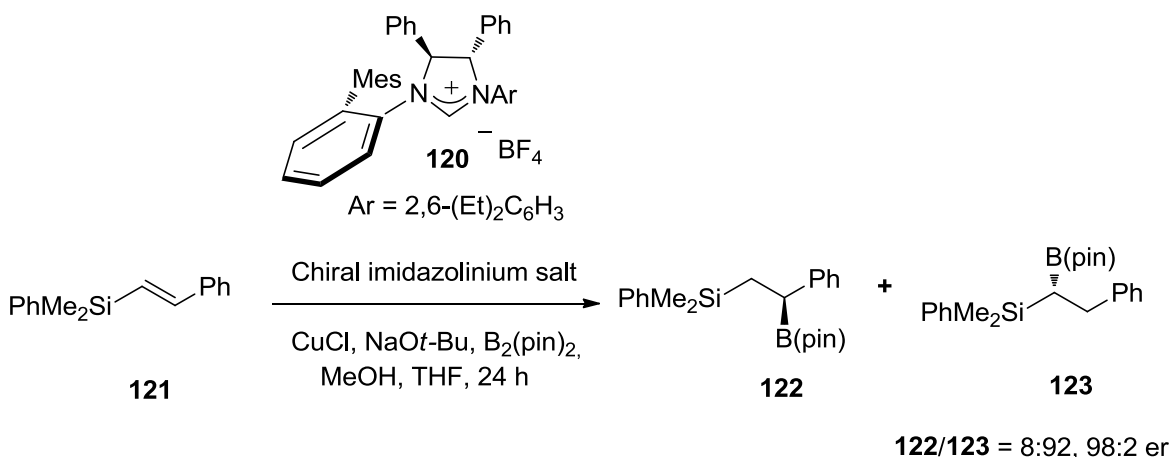
Scheme 24. Intramolecular α -arylation of anilides catalyzed by *N*-heterocyclic carbene derived from **12**.³⁴

Hartwig and co-workers highlighted the application of a large number of chiral ligands in Pd-catalyzed intramolecular α -arylation of anilides to give 3,3-disubstituted oxindoles.⁴⁰ In this case, chiral bidentate phosphine ligands did not give good selectivity. Several groups tried to improve selectivity of this reaction including Glorius,⁴¹ but only moderate selectivity was obtained. Bulky *t*-Bu groups at the stereogenic centres to nitrogen gave moderate enantioselectivity. *Ortho*-substituents on the phenyl ring played key roles in the enantioselective formation of the product and obtained good enantioselectivity (**Scheme 25**).⁴²



Scheme 25. Several Pd-catalyzed asymmetric intramolecular α -arylation of anilides by using chiral NHC ligands.^{35,36,37}

An *E*-selective catalytic method for preparation of Si-containing alkenes through protosilylation of terminal alkynes was reported by Hoveyda.⁴³ They also demonstrated Cu-catalyzed copper–boron additions to vinylsilanes derivatives catalyzed by *N*-heterocyclic carbene copper complexes to generate vicinal or geminal borosilanes (**Scheme 26**).



Scheme 26. Formation of vicinal or geminal borosilanes catalyzed by an *N*-heterocyclic carbene.³⁸

1.3.2. *N*-Heterocyclic Carbene Metal Complexes

1.3.2.1. Historical perspective

Complex of **124** was the first example of transition metal carbene which was reported by Fischer and Maasböl.⁴⁴ Since their landmark report in 1964, transition metal carbene complexes in inorganic chemistry have become of great interest.

In 1968 the first syntheses of NHC metal complexes **125** and **126** were reported by Wanzlick and Öfele (**Figure 7**).^{31,45} Then Schrock in 1974, developed a new type of carbene with a different reactivity, called the Schrock carbenes,⁴⁶ which are identified by more nucleophilic carbene carbon centres; these species mainly feature higher valent metals.

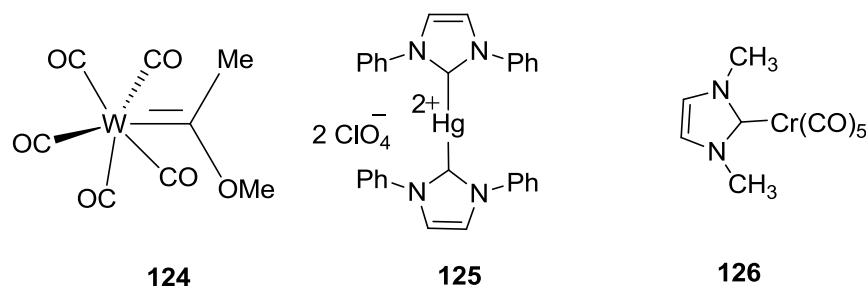


Figure 7. The first examples of a transition metal carbene complex.^{31,39,40}

N-Heterocyclic carbenes are σ -donor ligands, NHC ligands have been considered to be mainly inert. This inert property is the reason for their resistance to oxidation and thermal stability. In 1993, Öfele and co-workers showed that the metal-carbon bond in NHC complexes, trialkylphosphanes and alkylphosphinates have the same bonding properties.⁴⁷

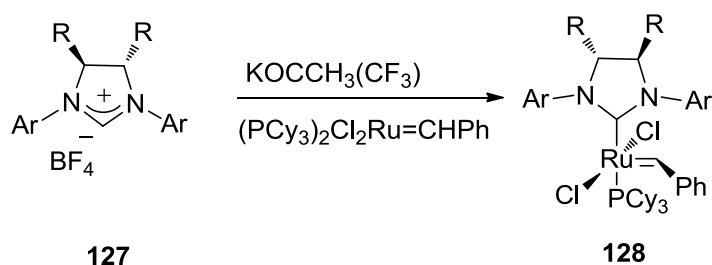
1.3.2.2. Complexation to Metals

Different synthetic routes have been discovered for the synthesis of NHC metal complexes such as using external base,⁴⁸ transmetalation,⁴⁹ oxidative addition⁵⁰ and co-condensation.⁵¹

Öfele utilized an anionic carbonyl hydride complex in the synthesis of the first M-NHC complex.⁴⁰ The basic metalate ion $[\text{HCr}(\text{CO})_5]^-$ deprotonated an imidazolium salt to afford the M-NHC complex. Du Pont reported the first 14-electron carbene complexes with two-fold coordinated Ni(0) and Pt(0) were synthesized in 1994 via reaction of a metal precursor with carbene in appropriate solution.⁵² Cloke reported the first homoleptic zerovalent carbene complexes by co-condensation of NHCs with metal vapor in reasonable yields.⁴⁶

The NHC complexes can also be synthesized by the reaction of imidazolinium or imidazolium salts with an external proper bases.⁴³

In the second generation of ruthenium-NHC complexes, Grubbs and co-workers highlighted deprotonation of the imidazolinium salts by using potassium hexafluoro-*tert*-butoxide as the external base, followed by direct complexation of the *in situ*-generated NHCs at room temperature (**Scheme 27**).⁵³

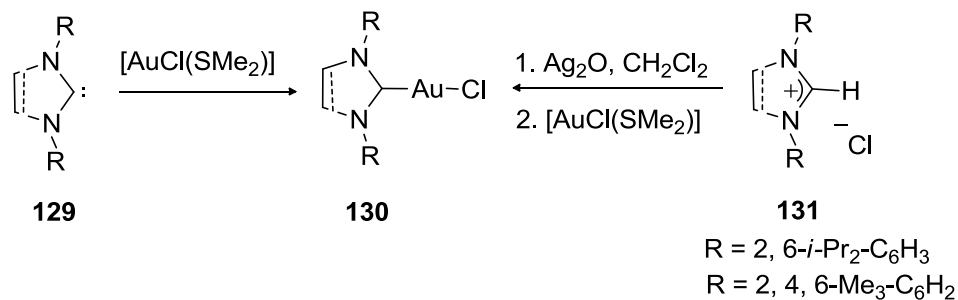


Scheme 27. Synthesis of NHC-complexes by deprotonation of imidazolinium salt with external base.⁴⁸

Silver *N*-heterocyclic carbene complexes have played an important role in the development of metal-carbene systems. Deprotonation of imidazolium or imidazolinium salt by use of a silver base has been the most widely used method in the synthesis of *N*-heterocyclic carbene complexes of silver. Silver NHCs could be synthesized from different silver sources. In 1997, Bertrand used silver acetate in the synthesis of a silver-NHC from triazolium salts.⁵⁴ In 2000, Danopoulos reported application of silver carbonate in the formation of silver NHCs.⁵⁵ In 2007, synthesis of silver NHCs by using Ag₂O was reported by Wang and co-workers.⁵⁶

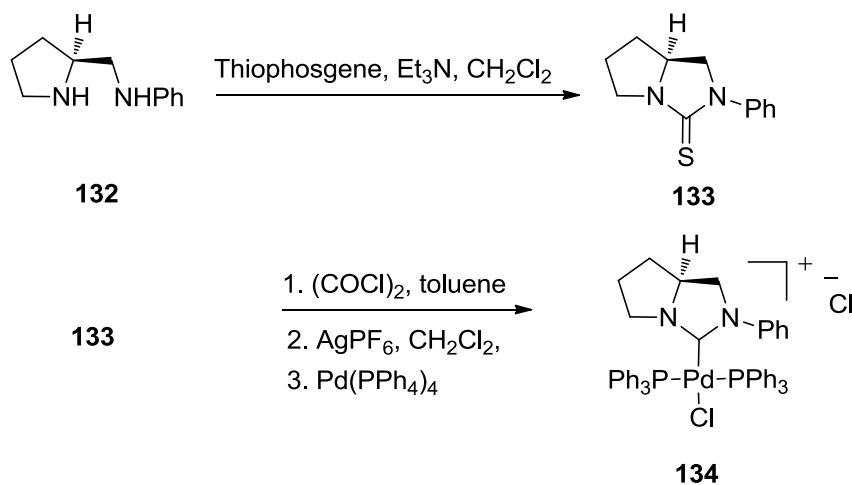
Silver *N*-heterocyclic carbenes have attracted much attention in the development of other NHC complex systems by way of transmetalation reactions. Transmetalation reactions using silver NHCs have been reported for a large number of transition metals: Ir(I), Ir(III), Cu(I), Cu(II), Pd(II), Ru(II), Ru(III), Ru(IV), Pt(II), Au(I), Rh(I), Rh(III), and Ni(II). Recent reviews dealing with transmetalation reactions

using silver NHCs have been published by Lin.⁵⁷ For example, Gimeno reported synthesis of silver(I)–NHC complexes for transmetalation to gold–NHC complexes (**Scheme 28**).⁵⁸



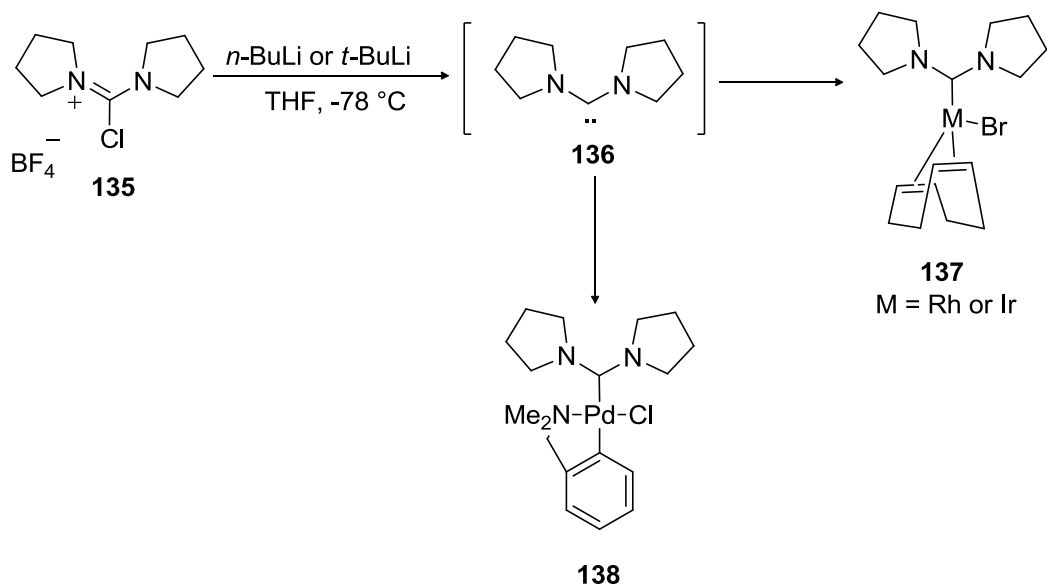
Scheme 28. Example of using silver (I) transmetalation in formation of NHC complexes.⁵³

Following oxidative insertion, metal–diaminocarbene complexes were synthesized by Fürstner and colleagues by oxidative insertion of $[\text{Pd}(\text{PPh}_3)_4]$ or $[\text{Ni}(\text{COD})_2]$ with PPh_3 into the C–Cl bond of 2-chloro-1,3-disubstituted imidazolinium salts (**Scheme 29**).⁵⁹



Scheme 29. Synthesis of NHC-complexes by oxidative addition.⁵⁴

A lithium-halogen exchange route has been used to prepare different kind of complexes via one pot transmetalation. This method has been developed by Hong and co-workers in the synthesis of acyclic diaminocarbenes via lithium-halogen exchange (**Scheme 30**).⁶⁰



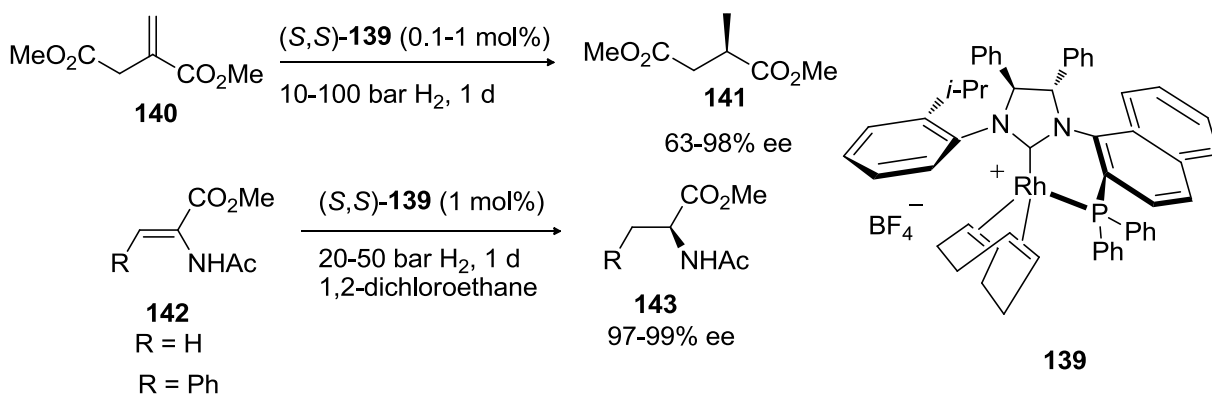
Scheme 30. Synthesis of NHC-complexes by a lithium-halogen exchange.⁵⁵

1.3.2.3. Application of NHC-complexes

In 1996 Enders applied chiral carbenes in the the first asymmetric intramolecular Stetter reaction.⁶¹ Since then, different kinds of chiral NHC ligands have been used in various asymmetric reactions. The following section will describe some examples of the application of chiral NHC ligands in asymmetric organic reactions. Several attempts have been performed for achieving good selectivity by using chiral NHC-complexes in asymmetric organic reactions. Several kinds of metals were used for the synthesis of NHC-complexes and applied in asymmetric organic reactions.

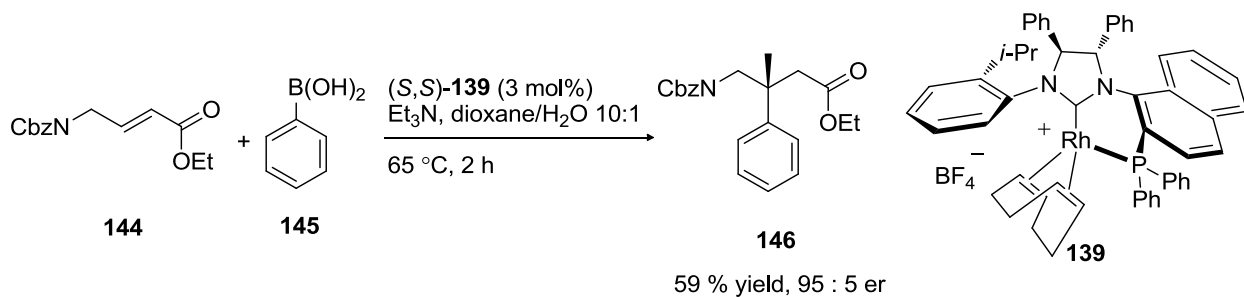
Several chiral rhodium-NHC complexes have been prepared and found useful in asymmetric organic reactions. Helmchen designed rhodium-NHC complexes with the combination of two different

backbones, including a rigid 2-(diphenylphosphino)naphthyl group connected to the dihydroimidazole moiety via a stereogenic axis to one nitrogen and a phenyl group with an *i*-Pr-substituent to the other nitrogen.⁶² These are disposed *anti*- to the phenyl groups of the dihydroimidazole moiety on another side in the asymmetric hydrogenation of substrates dimethyl itaconate and *N*-acetyldehydroamino acid derivatives (**Scheme 31**).



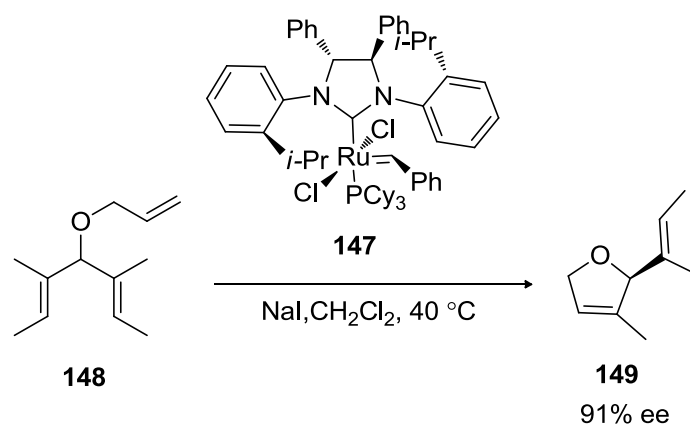
Scheme 31. Asymmetric hydrogenation catalyzed by (*S,S*)-**139**.⁵⁷

A year later, Helmchen used this catalyst in asymmetric conjugate additions of arylboronic acids to enones and α,β -unsaturated esters.⁶³ The results showed of arylboronic acids to enones and α,β -unsaturated esters excellent catalytic activity in conjugate additions of phenylboronic acids due to steric and electronic properties of the catalyst (**Scheme 32**).



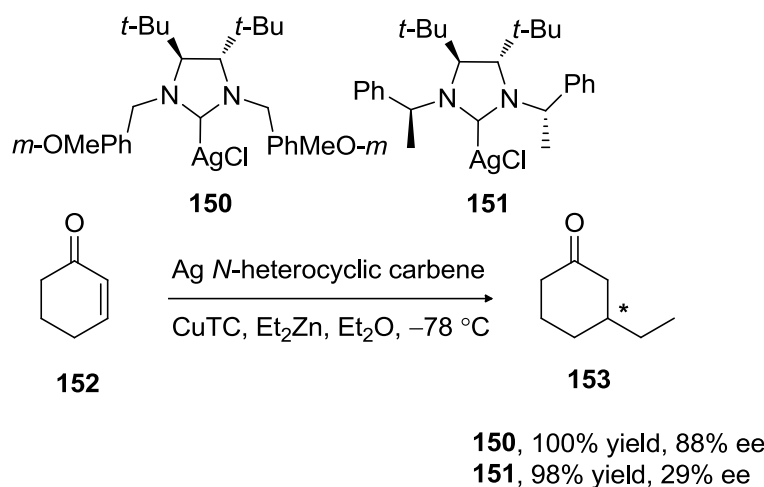
Scheme 32. Conjugate addition of phenylboronic acid to α,β -unsaturated ester catalyzed by (*S,S*)-**139**.⁵⁸

In 2005, Grubbs and co-workers won the Nobel Prize for development of olefin metathesis in organic reactions. Grubbs reported the first enantioselective olefin metathesis by using NHC catalysts in the desymmetrization of achiral trienes with high enantiomeric excess (**Scheme 33**).⁵⁰



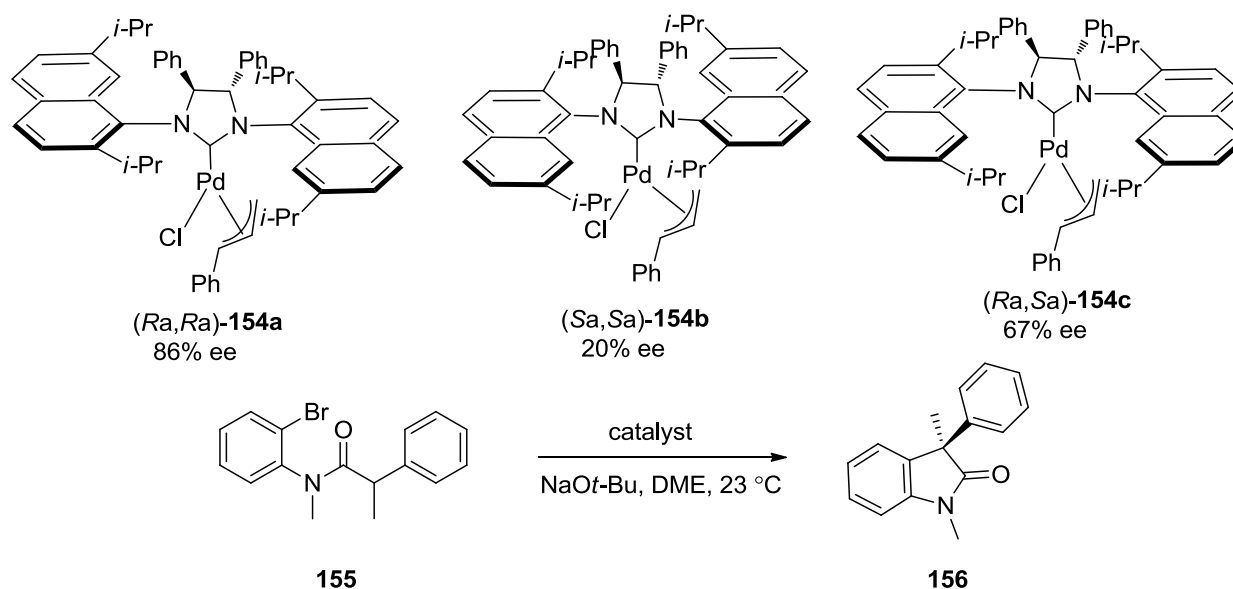
Scheme 33. Desymmetrization of achiral trienes catalyzed by Grubbs' catalyst.⁵⁰

Several *N*-heterocyclic carbene ligands have been applied in the copper catalyzed 1,4-addition of a dialkylzinc reagent to an unactivated β -substituted cyclicenones.⁶⁴ Recently, selective allylic substitutions by using copper derivatives and Grignard or dialkylzinc reagents catalyzed by *N*-heterocyclic carbenes as ligands have been reported.⁶⁵ Roland and Alexakis reported an enantioselective copper catalyzed 1,4-conjugate addition reactions by using chiral diaminocarbenes as ligands in silver complexes.⁶⁶ Analysis of the catalytic data demonstrated the effect of low temperature conditions using diethyl ether and CuTC was superior in terms of enantiomeric excess for this reaction, and also higher selectivity was observed when they employed the *m*-OMe substituted analogue **151**. The corresponding adduct was obtained in a 100% yield with an enantiomeric excess of 88% (**Scheme 34**).



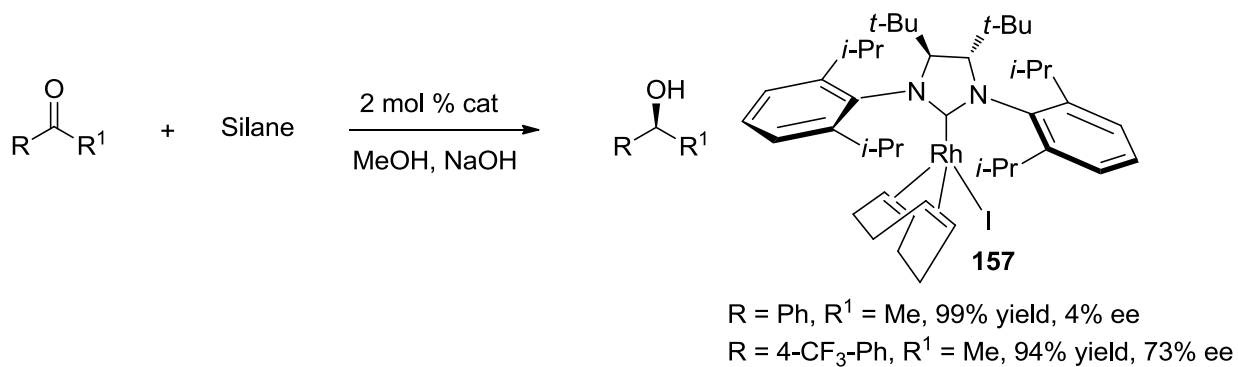
Scheme 34. Addition of Et_2Zn to cyclohexenone catalyzed by **150**, **151**.⁶¹

An attempt to synthesize NHC-palladium complexes with a chiral *N*-heterocycle and naphthyl side chains by Dorta gave three different isomers, which were separated successfully and applied in the asymmetric intramolecular α -arylation of amides, leading to the formation of oxindoles containing quaternary carbon centres in high yield and high enantiomeric purity.⁶⁷ The results showed that orientation of the aromatic side chains had an effect on selectivity in this reaction. Oxindoles with quaternary carbon centres were formed with high yield and selectivity (86% ee) when [(*Ra,Ra*)-**154**] was applied (**Scheme 35**).



Scheme 35. Intramolecular α -arylation of amides catalyzed by NHC-palladium complexes **154**.⁶²

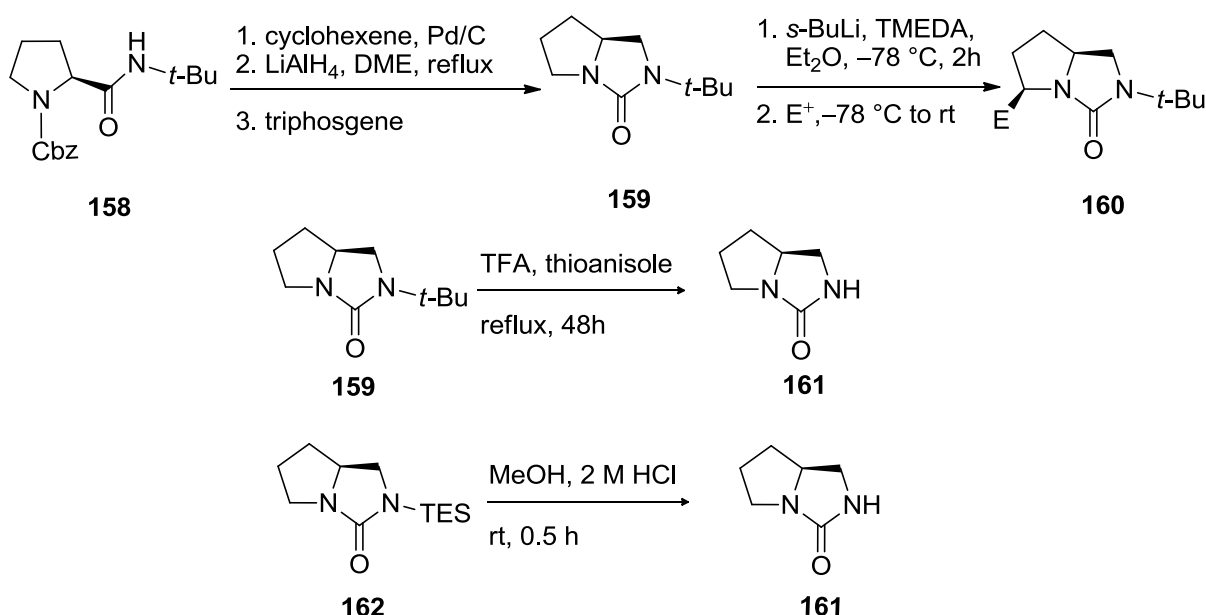
The first example for the application of chiral rhodium(I)-NHC complexes as enantioselective hydrosilylation catalysts was reported by Herrmann and co-workers.⁶⁸ In 2009, they considered the catalytic activity and selectivity of the rhodium(I) complex for the hydrosilylation of prochiral ketones. The result showed only significant enantioselectivity (73% ee) being obtained with 4-(trifluoromethyl)acetophenone at ambient temperature (**Scheme 36**).⁶⁹



Scheme 36. Hydrosilylation of prochiral ketones by catalyst **157**.⁶⁴

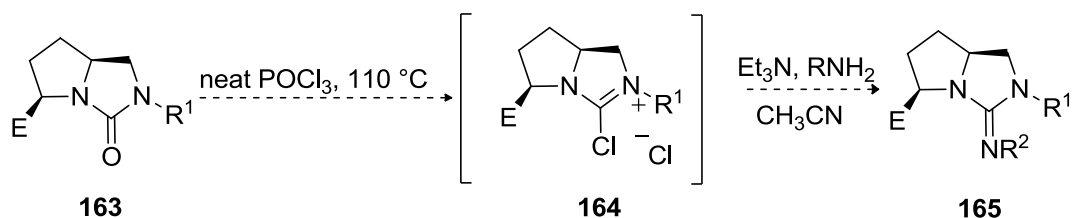
1.4. Aims and Objectives

There have been a number of previous attempts via lithiation–substitution of *t*-Bu protected ureas to afford series of C5-substituted products with *syn* stereochemistry,⁷⁰ but there were two challenges in synthesis of *N*-substituted products. The first challenge was generation of inconstant yields upon scale up. The second was the harsh reaction conditions required for deprotection of the C5-substitution product **159**, such as reflux for 48 hours with trifluoroacetic acid, which posed stability issues in some derivatives.⁶⁵ These issues encouraged us to explore a viable synthetic method to synthesize an *L*-proline hydantoin-derived *N*-silyl protected version of **159**, which undergoes analogous diastereoselective lithiation and substitution to obtain substituted products that may be readily *N*-desilylated with dilute acid at room temperature to generate secondary ureas (**Scheme 37**).



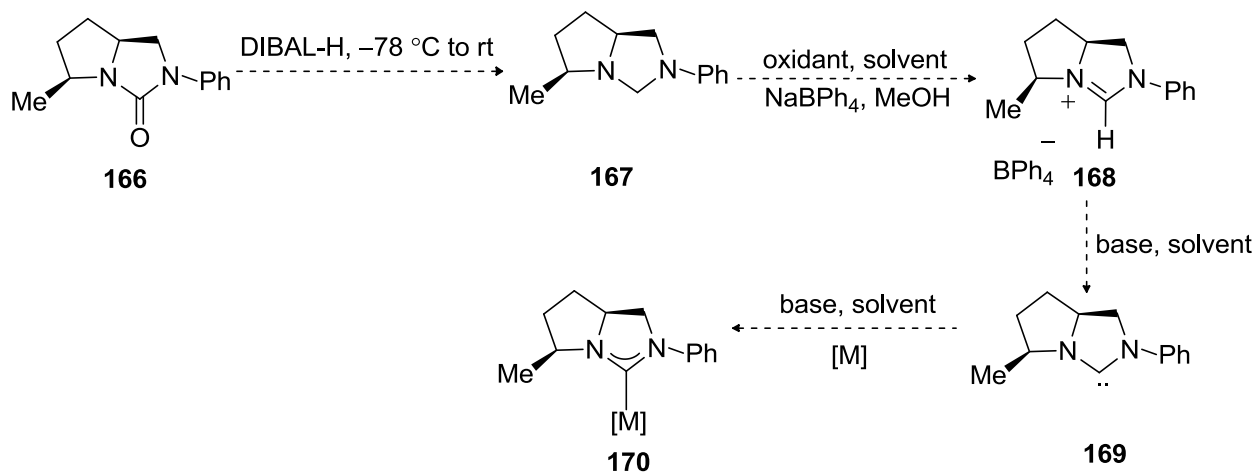
Scheme 37. *N*-deprotection of compounds **159** and **162**.

The ureas **163** undergo *N*-arylation leading to chiral pyrroloimidazolinones, which undergo POCl₃ or (COCl)₂ activation to generate the target biological active compounds. Treatment of compound **163** with POCl₃ will afford chiral annulated chloroimidazolinium salts **164**, which can be applied as an intermediate for the synthesis of chiral guanidines **165** by using the appropriate amines (**Scheme 38**).



Scheme 38. Proposed method to synthesize guanidine **165**.

The chiral urea **166** will also be converted to the compound **167** via reduction by DIBAL-H in THF at $-78\text{ }^\circ\text{C}$. The chiral amina **167** will undergo salt formation by oxidation to give **168**, which may serve as a precursor to NHC **169** by using external base. The resulting NHC ligands will be used for formation of transition metal complexes **170** (Scheme 39).

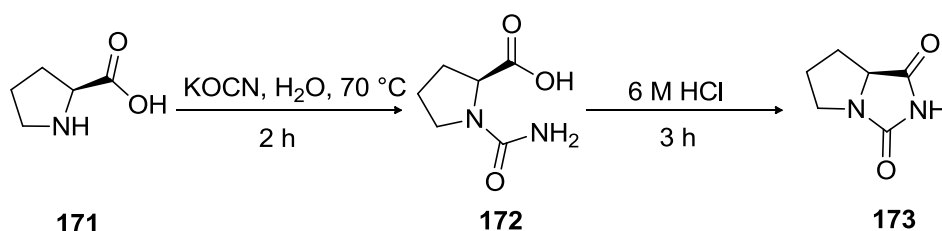


Scheme 39. Proposed method to synthesize complex **170**.

2. Results and Discussion

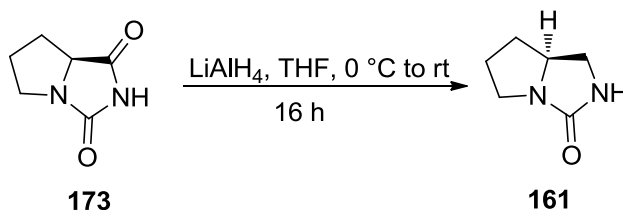
2.1. Preparation of 2-Triethylsilyl-hexahydro-pyrrolo[1,2-c]imidazol-3-one

The *L*-proline hydantoin is synthesized from readily available starting materials and its application as a precursor to a chiral auxiliary for diastereoselective lithiation of ferrocenes⁷¹ made it an attractive starting material for the synthesis of C5-substituted imidazolinones. *L*-proline hydantoin was prepared easily from *L*-proline **171** in the presence of potassium cyanate in water, followed by treatment with 6 M aqueous HCl in 61% yield (**Scheme 40**).⁷²



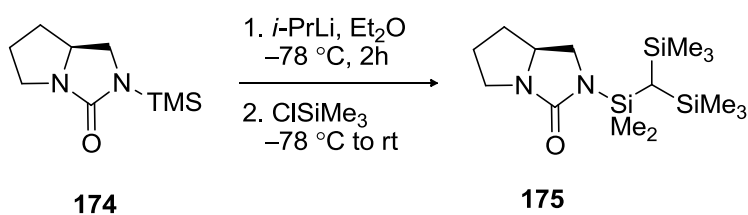
Scheme 40. Synthesis of *L*- proline hydantoin from *L*-proline.⁷³

The proline hydantoin was reduced with lithium aluminium hydride in THF at room temperature⁷³ to give compound **161** in moderate yield (56 %). Compound **161** was prepared in large-scale without racemization of the pyrrolidine chiral centre (**Scheme 41**).



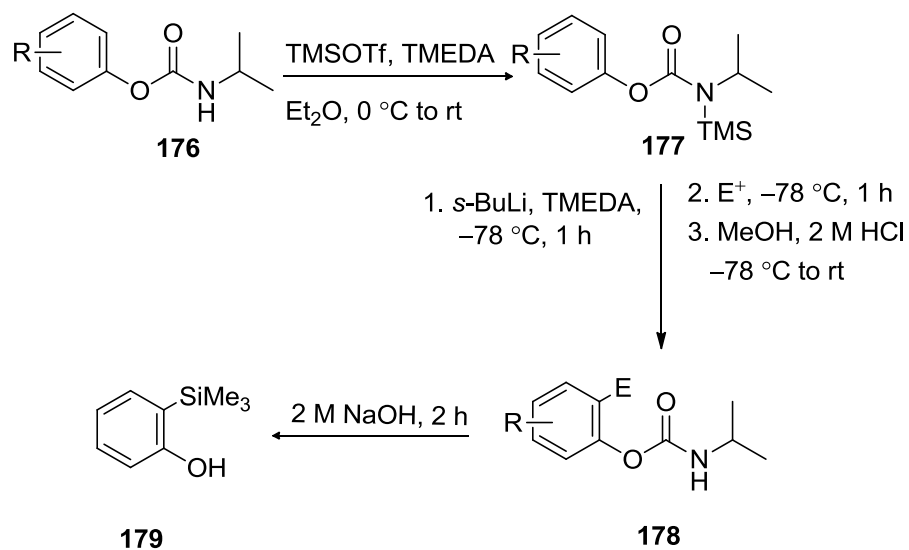
Scheme 41. Synthesis of compound **161**.

Based on previous research in *ortho* lithiation by Hoppe,⁷⁴ imidazolinone **161** was initially *N*-protected by deprotonation of nitrogen with *i*-PrLi/TMEDA, followed by addition of TMSCl. Although product **174** was air-stable and could be purified by flash column chromatography, subsequent attempts to induce diastereoselective lithiation at the C5 position by sequential treatment with *i*-PrLi and TMEDA at $-78\text{ }^{\circ}\text{C}$ in diethyl ether, followed by TMSCl quench, resulted in the formation of the *N* [bis(trimethylsilyl)methyl]dimethylsilyl product **175** (Scheme 42).



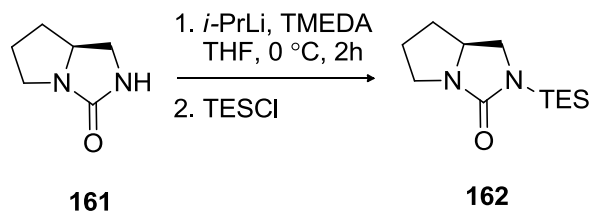
Scheme 42. Formation of *N*-[bis(trimethylsilyl)methyl]dimethylsilyl compound **175**.

The observed regiochemistry was presumably due to the greater acidity of the α -silylmethyl groups over the C5 position. This result was in contrast with the behavior of *N*-trimethylsilyl protected aryl-*O*-carbamate **177** reported by Hoppe,⁶⁹ which gave phenol **179** by *ortho* lithiation after electrophile quench, deprotection and hydrolysis of the secondary carbamate **177** (Scheme 43).



Scheme 43. *N*-trimethylsilyl protected aryl-*O*-carbamate **177**.⁶⁹

To prevent α -silyl carbanion formation, triethylsilyl chloride was used with the expectation that the α -silyl methylene groups would be less prone to deprotonation (**Scheme 44**).



Scheme 44. *N*-protection of compound **161**.

2.2. Diastereoselective Lithiation-Substitution of Compound 159

Computational studies were done on **159** to determine the distances between the urea oxygen atom and the pro-*S* and pro-*R* alpha methylene hydrogens. The results showed that the pro-*S* proton alpha

to nitrogen was closer to the carbonyl oxygen (2.505 Å) compared to the pro-*R* proton (3.692 Å);¹³ lithiation will take place at the pro-*S* proton over the pro-*R* proton because of the shorter distance between the alkyllithium base to that hydrogen upon coordination to oxygen (red = oxygen, blue = nitrogen, white = hydrogen, grey = carbon) (**Figure 8**). The structure of compound **159** was optimized at the B3LYP/6-31G(d) level as implemented in Gaussian 03.¹³

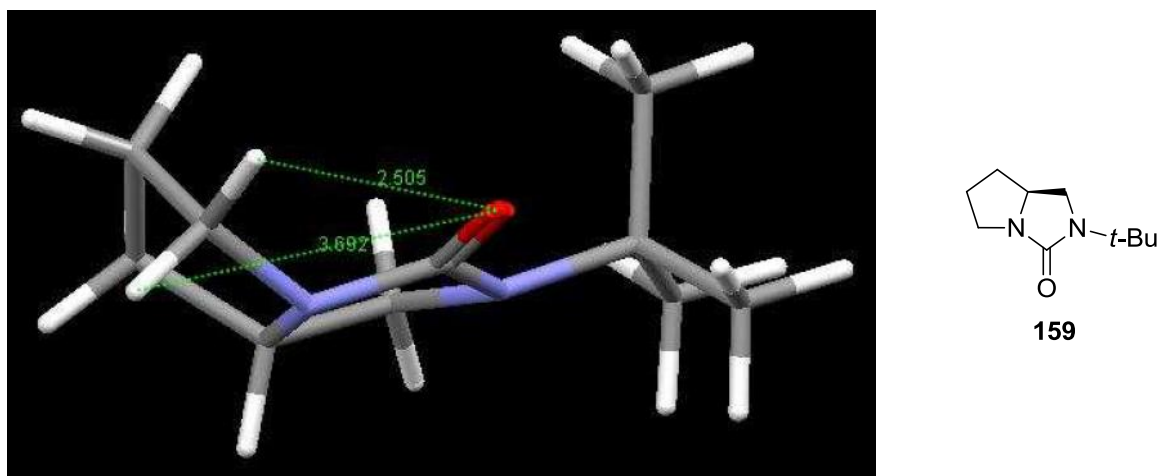
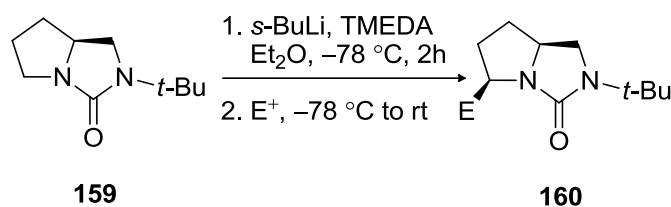


Figure 8. Minimum energy structure of **159**.¹³

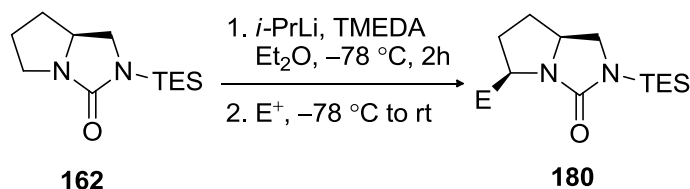
The first attempt of diastereoselective lithiation of compound **162** was done by using *i*-PrLi and TMEDA and Et₂O in -78 °C followed by electrophilic quench. *sec*-BuLi was also examined for this reaction based on previous research, which was done by our group for diastereoselective lithiation of *tert*-butyl *N*-protected urea (2-*tert*-butyl-hexahydro-pyrrolo[1,2-*c*]imidazol-3-one) **159** (**Scheme 45**).¹³



E = Ph₂COH, Me, allyl, SnMe₃, SiMe₃, CO₂H

Scheme 45. Diastereoselective lithiation of compound **159**.¹³

Several electrophiles were used for diastereoselective lithiation of compound **162** (**Scheme 46**), such as dimethyl sulfate, trimethylsilyl chloride, benzophenone and tributyltin chloride (**Table 1**). These reactions gave moderate to good yields and single diastereomers, which were determined by ¹H and ¹³C NMR analysis. All obtained products are exclusively in the *syn* configuration, which is proven by NOE spectroscopy.



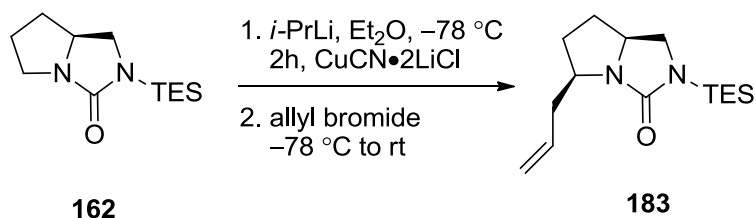
Scheme 46. Diastereoselective lithiation of compound **162**.

Table 1. Results of diastereoselective lithiation of compound **162**.

compound	E ⁺	E	yield %
181	Me ₂ SO ₄	Me	65
182	Ph ₂ CO	C(OH)Ph ₂	61
183	allyl bromide*	allyl	47
184	SiMe ₃ Cl	SiMe ₃	86
185	SnBu ₃ Cl	SnMe ₃	60

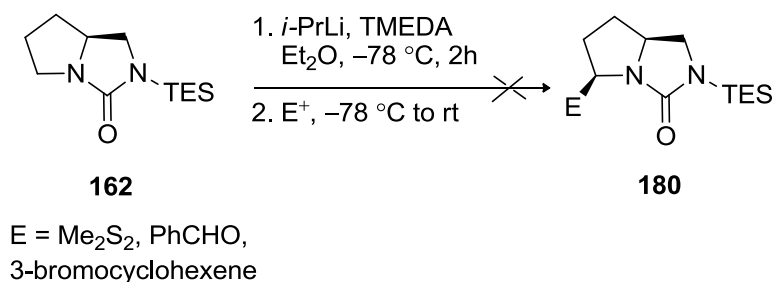
*via CuCN·2LiCl transmetalation.

Allylation of **162** by transmetalation of the alpha lithio intermediate with a mixture of copper cyanide and lithium chloride in the presence of TMEDA gave 31% yield. Surprisingly, a slightly better yield was obtained when the reaction was performed without TMEDA (47%) (**Scheme 47**).



Scheme 47. Transmetalation of alpha lithio intermediate for allylation.

Several attempts were made with different kinds of electrophiles such as benzaldehyde, dimethyl disulfide and 3-bromocyclohexene, but no product was produced (**Scheme 48**).



Scheme 48. Several attempts to diastereoselective lithiation

Several reaction conditions were examined to optimize the reaction conditions. For example, different kinds of lithium species and solvents were tested. The results showed that *i*-PrLi and Et₂O were superior in terms of yield in the diastereoselective lithiation reaction. Stereochemistry of all these products was confirmed by NMR spectroscopy. For example, analysis of **181** by HSQC showed the proton connected to the corresponding carbon atom to identify the proton-carbon connectivities, then NOSEY or NOE showed that the methine protons of interest of chiral centres were on the same side of the molecule, a correlation cross peak between these same methine protons of chiral centres (indicated by arrows) was obtained (**Figure 9**).

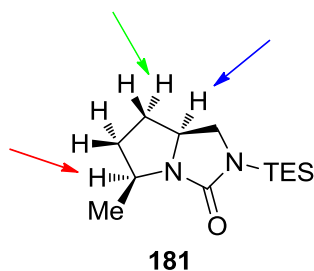
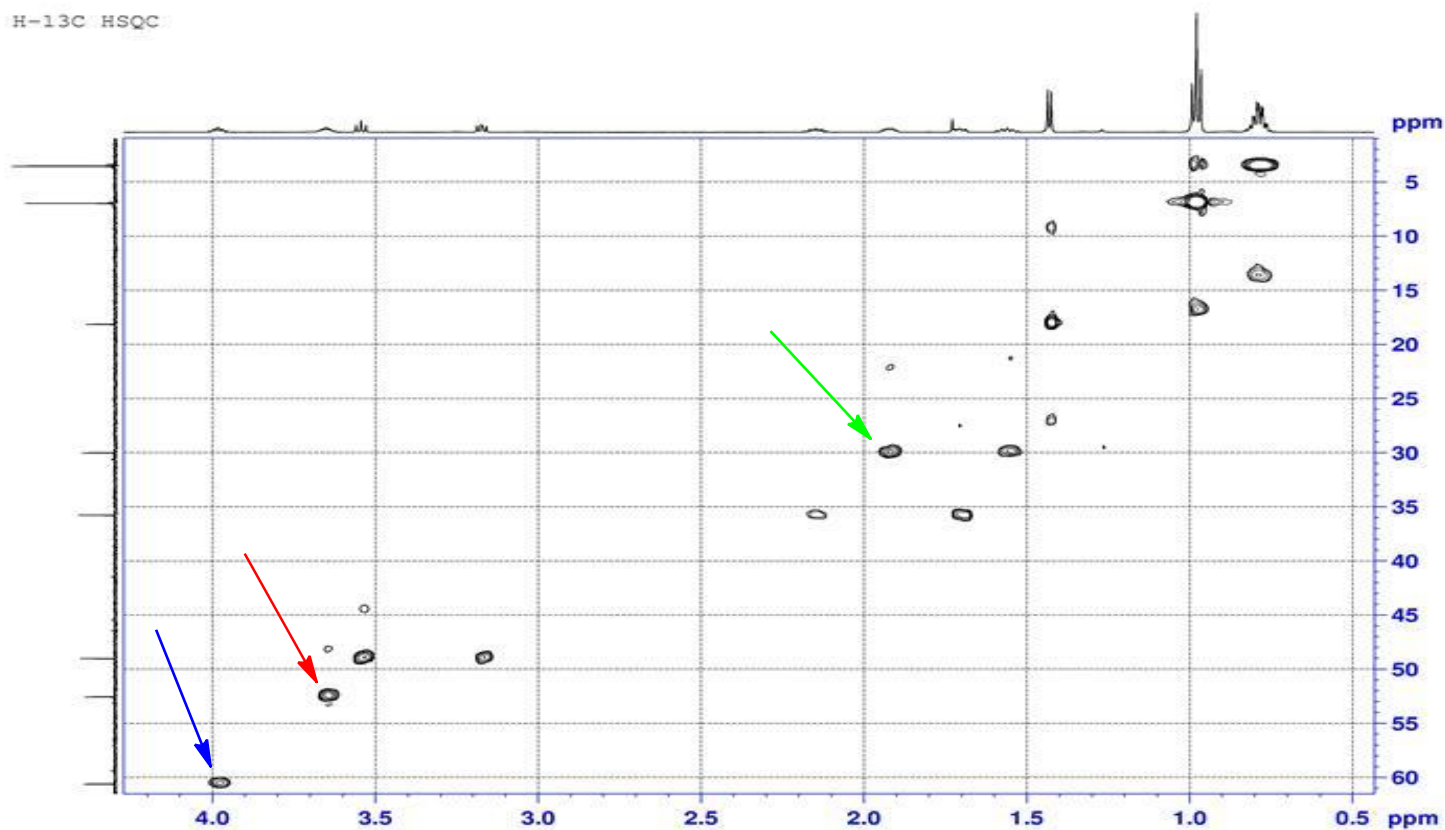


Figure 9.HSQC spectrum of **181**.

For example, in the 1D-NOE of **181**, irradiation of a proton from the pyrrolidine methine groups at 1.91 led to enhancements of the key methane proton (indicated by arrows) at 3.98 and irradiation of a proton at 3.98 lead to enhancement of the key methane protons at 3.69 and 1.91 ppm respectively (**Figure 10**). Similar enhancements were observed in the 1D-NOE spectra of **182**, **183**, **184**, **185**.

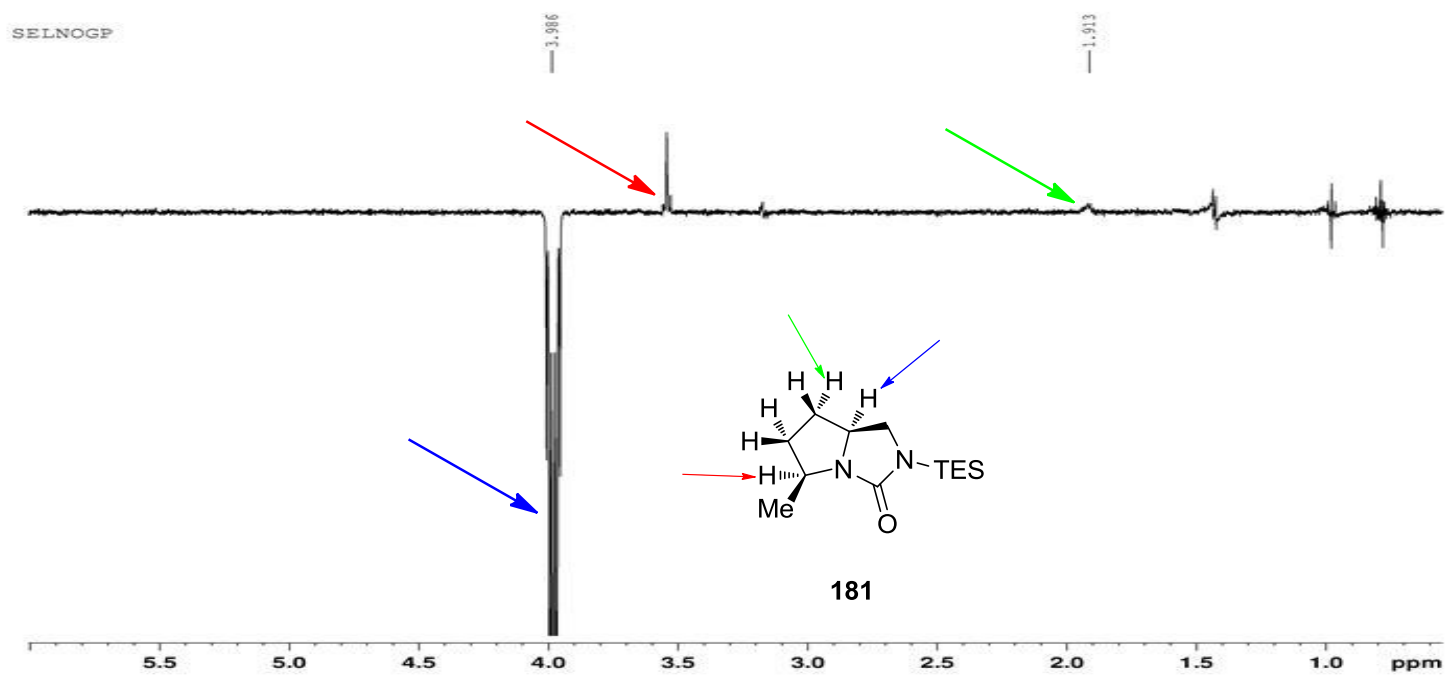
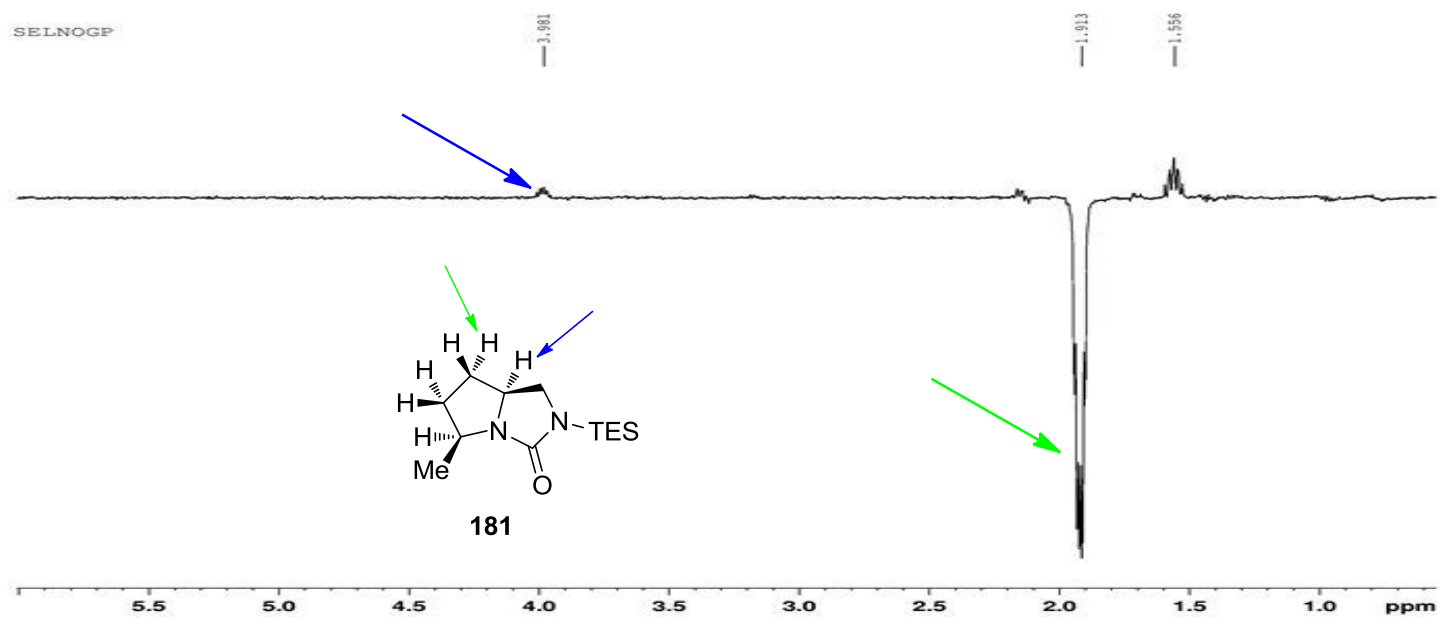


Figure 10. 1D-NOE of 181.

2.3. *N*-Desilylation of secondary ureas

Deprotection of the *N*-*t*-Bu group on the C5-substituted compound **159** requires harsh reaction conditions, such as using trifluoroacetic acid in reflux for 48 hours, which may lead to stability issues for certain derivatives (**Scheme 37**).¹² Products **181-185** underwent smooth *N*-desilylation upon treatment with 2M aqueous HCl for 30 min at room temperature to give secondary ureas **186-190** in good yields (71-91%). It is notable that potentially sensitive substituents, such as the diphenylhydroxymethyl group of **182** or the stannane of **185**, remained intact under these conditions (**Table 2**).

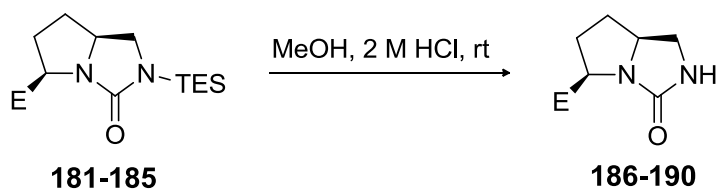
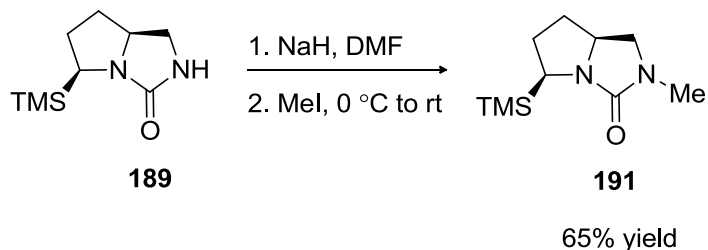


Table 2. Results of *N*-desilylation.

compound	product	E	Yield %
181	186	Me	84
182	187	Ph ₂ COH	80
183	188	allyl	82
184	189	SiMe ₃	91
185	190	SnBu ₃	71

2.4. N-Alkylation

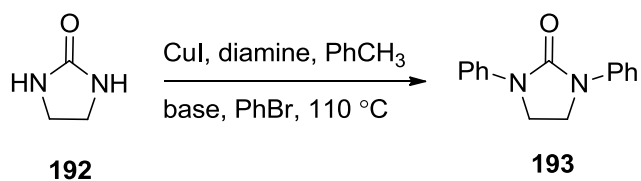
The ability to remove the *N*-TES group in the preceding products allows for the introduction of new *N*-substituents. For example, compound **189** underwent *N*-alkylation by using sodium hydride and methyl iodide in DMF at 0 °C to room temperature (**Scheme 49**).



Scheme 49. *N*-alkylation of compound **189**.

2.5. N-Arylation

Leung reported synthesis of symmetrical and unsymmetrical *N*-aryl-substituted cyclic ureas by employing copper(I) iodide and ligand in toluene in the presence of base (**Scheme 50**).⁷⁵ Leung mentioned that ligands play an important role in the reactivity of copper catalysts in this reaction. They examined different ligands such as *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine (DMCHDA) and *trans*-cyclohexane-1,2-diamine (CHDA) with different bases and solvents (**Table 3**).

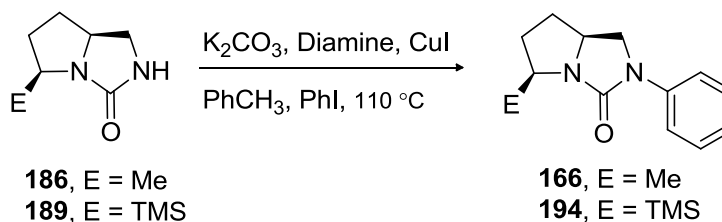


Scheme 50. Synthesis of *N*-aryl-substituted cyclic urea **193**.⁷⁰

Table 3. Results of the *N*-arylation of cyclic urea **193**.⁷⁰

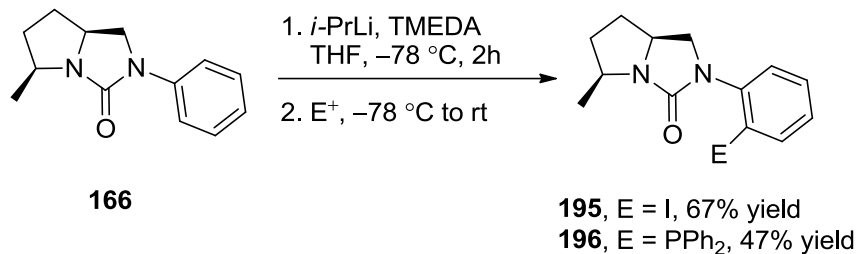
Entry	Base	Diamine ligand	Yield (%)
1	K ₃ PO ₄	CHDA	2
2	K ₂ CO ₃	CHDA	62
3	Cs ₂ CO ₃	CHDA	19
4	K ₃ PO ₄	DMCHDA	54
5	K ₂ CO ₃	DMCHDA	92
6	Cs ₂ CO ₃	DMCHDA	44

A Goldberg–Buchwald–Nandakumar C–N coupling, using different diamine ligands, such as cyclohexane-1,2-diamine (CHDA) and tetramethylethylenediamine (TMEDA), with copper(I) iodide, potassium carbonate, iodobenzene in toluene at 110 °C for 48 h, provided the desired coupling product (**Scheme 51**). *N*-Arylation of compounds **186** and **189** by employing CHDA gave low yields (5-20%). *N*-phenylation of either **186** or **189**, with a mixture of copper iodide and TMEDA, gave better yields (40-74%) (**Table 4**).

**Scheme 51.** *N*-Arylation of compound **186** and **189**.**Table 4.** Results of *N*-arylation of compounds **186** and **189**.

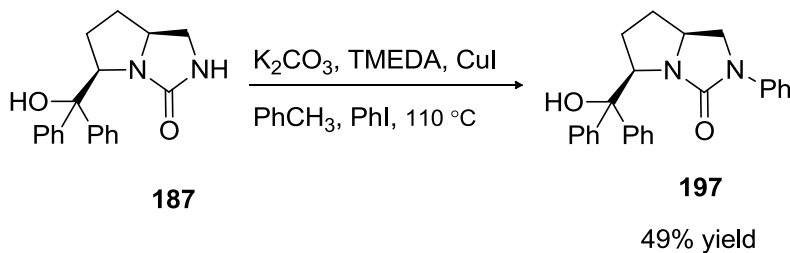
Entry	Compound	Diamine ligand	Product	Yield (%)
1	186	CHDA	166	20
2	189	CHDA	194	5
3	186	TMEDA	166	74
4	189	TMEDA	194	40

Lithiation of compound **166**, using *i*-PrLi in the presence of TMEDA in THF at $-78\text{ }^{\circ}\text{C}$ followed by electrophilic quenching, gave the desired *ortho*-substituted product (**Scheme 52**). Compounds **195** and **196** were obtained in 67% and 47% yields. Asymmetric lithiation with other lithium species, such as *n*-BuLi and *t*-BuLi, failed.



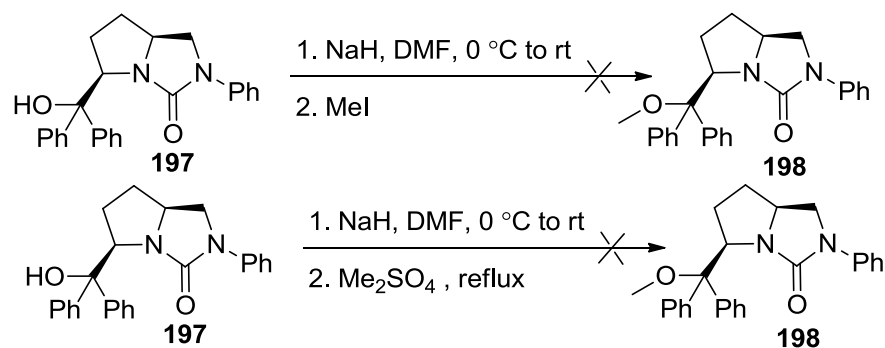
Scheme 52. Synthesis of *ortho* substituted ureas **195** and **196**.

N-Arylation of the bulky urea **187** under the same conditions as **Scheme 52** gave compound **197** in a 49% yield (**Scheme 53**).



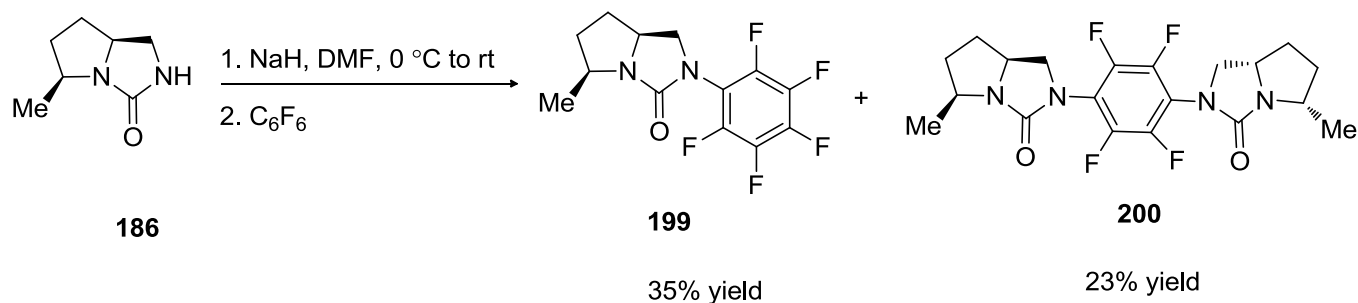
Scheme 53. *N*-Arylation of compound **187**.

The hydroxyl group of **197** was subjected to protection to prevent side reactions of the hydroxyl group in the next step, which consists of guanidine formation with POCl_3 . Protection of the hydroxyl group in compound **197** via alkylation with an excess amount of methyl iodide at room temperature failed. Protection of the hydroxyl group also failed using dimethyl sulfate under reflux conditions (**Scheme 54**).



Scheme 54. Attempted protection of compound **197**.

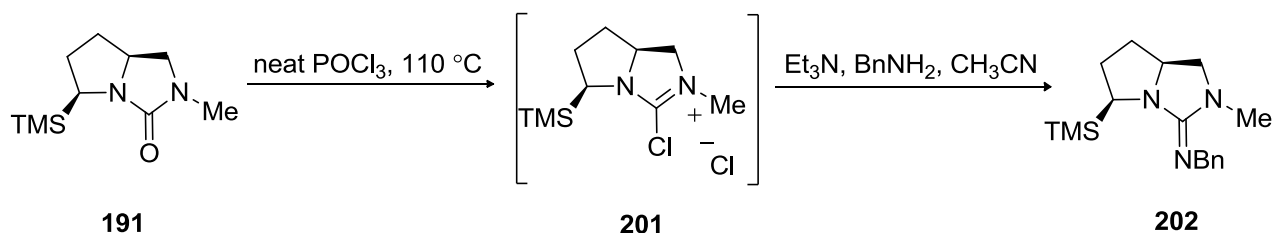
Compound **199** was synthesized with hexafluorobenzene and sodium hydride in DMF, due to significant rate enhancement in the catalytic performance of metal–NHC catalysts bearing fluorinated aryl groups on the NHC ligand.⁷⁶ We observed the formation of compound **199** in 35 % yield and by-product **200** in 23% yield (**Scheme 55**).



Scheme 55. Synthesis of compound **199** and **200**.

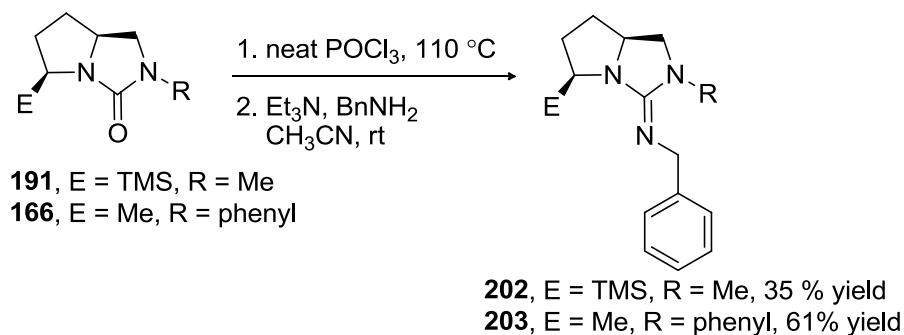
2.6. Guanidine Formation by POCl₃ Activation and Their Applications in Catalysis

Compound **191** was converted to the 3-chloroimidazolinium salt by using excess amounts of neat phosphoryl chloride at 110 °C. In this process, the intermediate 3-chloroimidazolinium salt **201** could not be isolated, and was therefore exposed without further purification to benzyl amine and triethylamine in acetonitrile to give the desired guanidine **202** (**Scheme 56**).



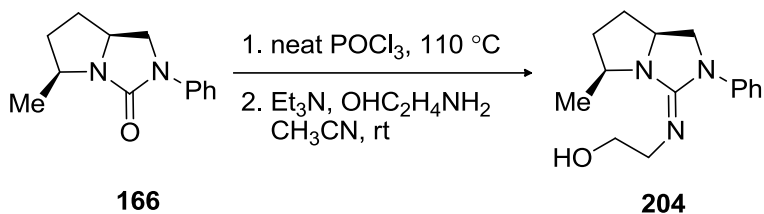
Scheme 56. Synthesis of guanidine **202** by POCl₃ activation.

The guanidine formation of compounds **202** and **203** by using ureas **166** and **191** gave moderate yields of 35% and 61%, respectively (**Scheme 57**). The ¹H NMR analysis showed a large number of broad peaks, which converted to the clear corresponding peaks after heating at 120 °C. This process indicated the presence of two isomers for compounds **202** and **203**, which were slowly interconverting via isomerization about a C=N bond via an inversion of the nitrogen substituent.



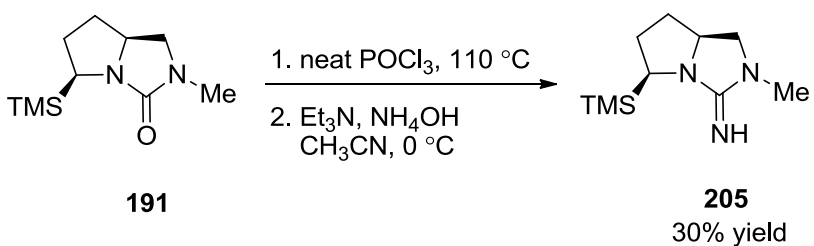
Scheme 57. Synthesis of guanidines **202** and **203**.

Guanidine **204** bearing a hydroxyl group was obtained in 31% yield to use of hydrogen bonding interactions to accelerate and control organic reactions, and also this hydrogen bonding can be used to stabilize anionic intermediates and transition states (**Scheme 58**).



Scheme 58. Synthesis of compound **204**.

Compound **205** was synthesized by using aqueous ammonia and triethylamine in 30% yield (**Scheme 59**). Then ureas **166** and **194** were converted into the corresponding guanidine products by the same synthetic method as used in the synthesis of **205**. This reaction gave **206** and **207** in 41% and 34% yields (**Table 5**).



Scheme 59. Synthesis of guanidine **205**.

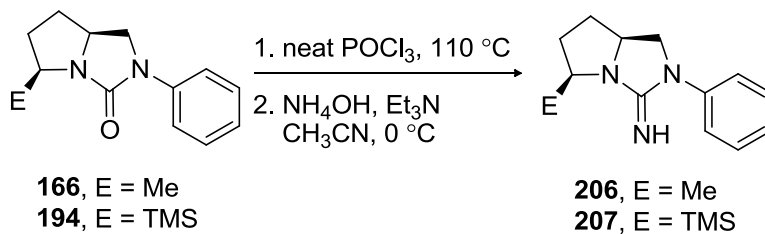
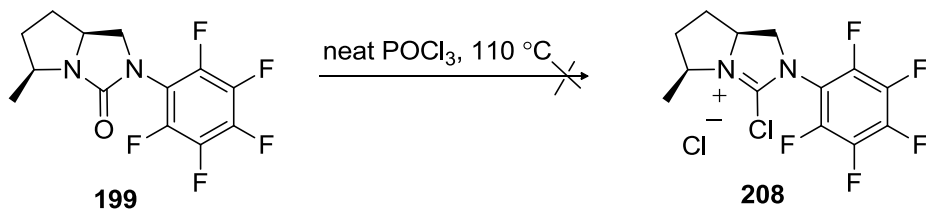


Table 5. Results of synthesis of compounds **206** and **207**.

Entry	compound	Yield (%)
1	206	41
2	207	34

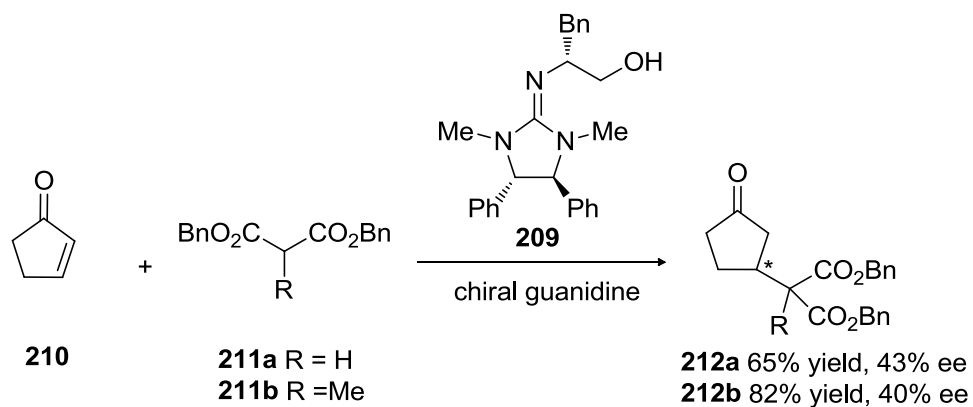
The formation of compound **208** in neat POCl₃ at 110 °C failed and only the starting material was recovered (**Scheme 60**).



Scheme 60. Attempted salt formation of compound **199**.

2.7. Application of Guanidines

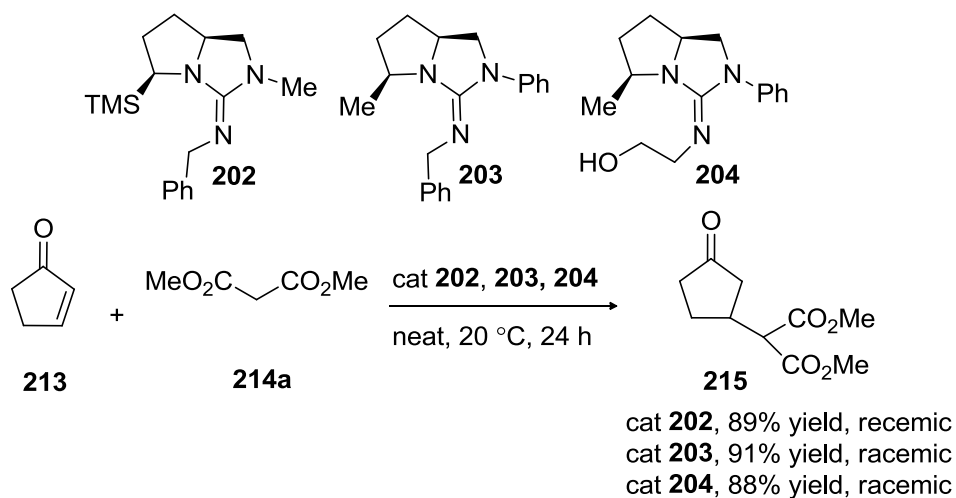
Previous studies by Ishikawa and co-workers showed that the Michael addition of cyclopentenone with dibenzyl malonates catalyzed by guanidine **209**, resulted in moderate to good asymmetric inductions (**Schemes 61, 11**).⁷⁷



Scheme 61. Reaction of cyclopentenone with dibenzyl malonates catalyzed by guanidine **209**.⁷²

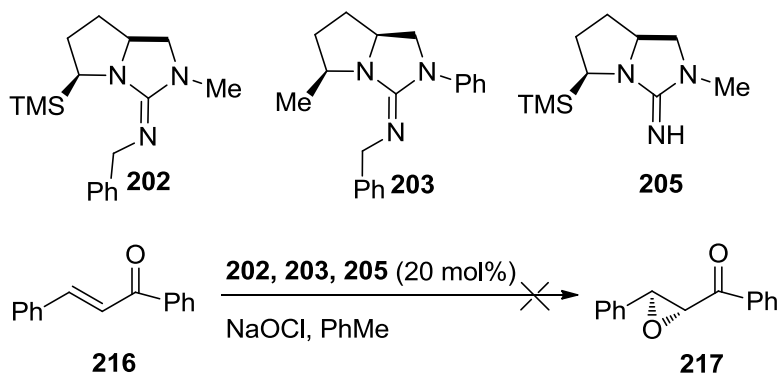
To improve the enantioselectivity of the reaction depicted in (**Scheme 61**) by addition of a chiral centre at alpha position and also presence a hydroxyl group functionality at catalysts, guanidines **202**,

203 and **204** were employed in the Michael addition of dimethyl malonate with cyclopentenone in solvent free conditions. The results gave only racemic products (**Scheme 62**). Optical rotation measurements were used to determine the enantioselectivity of the products.



Scheme 62. Michael addition of cyclopentenone with dimethyl malonate catalyzed by guanidines **202**, **203** and **204**.

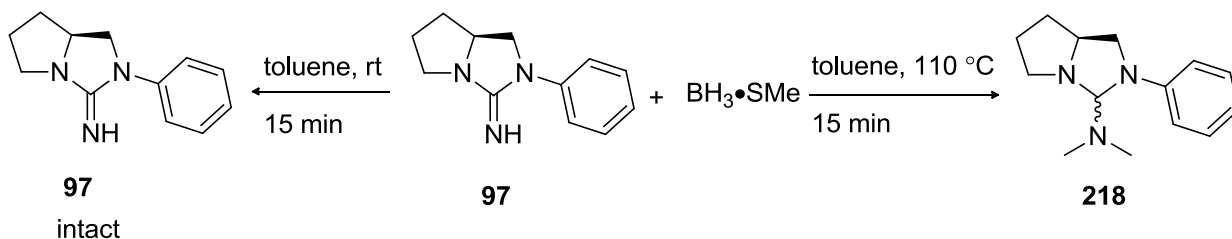
Guanidines **202**, **203** and **205** were applied to the epoxidation of chalcone by using sodium hypochlorite in toluene. The product was not formed and only the starting material was recovered (**Scheme 63**).



Scheme 63. Attempts at epoxidation of chalcone catalyzed by guanidines **202**, **203**, **205**.

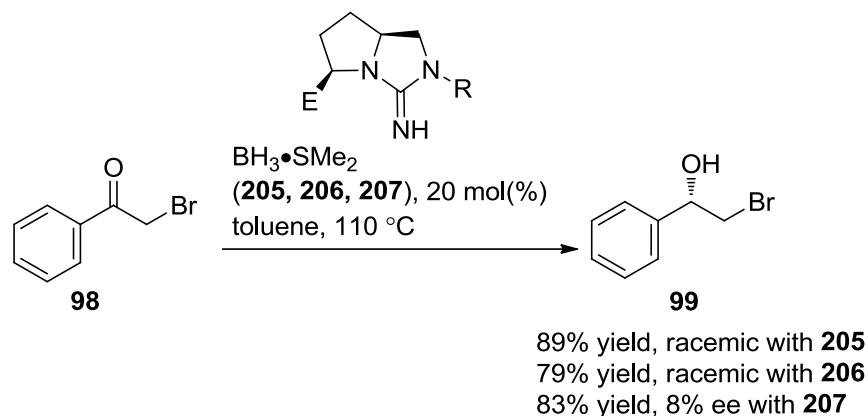
Previous studies by Basavaiah and co-workers²⁹ showed that borane-mediated reduction of phenacyl bromide **98** catalyzed by guanidine **97** (**Scheme 5**) to generate corresponding alcohol.

In order to understand the stability of the guanidine moiety in the presence of $\text{BH}_3\cdot\text{SMe}_2$, Basavaiah and co-workers treated guanidine derivatives and $\text{BH}_3\cdot\text{SMe}_2$ in toluene at room temperature for 15 min in a ratio of 1:20. The ^{13}C NMR spectrum showed that the guanidine moiety remained intact as demonstrated by; peaks in the region between δ 70-110 and the presence of a peak at 162.0 ppm, belonging to carbon nitrogen double bond were unchanged. However, when the reaction was performed in toluene under reflux conditions, they observed the presence of a peak at δ 85.0 ppm and absence of a peak at 162.0 ppm, which verifies that a reaction occurred (**Scheme 64**).



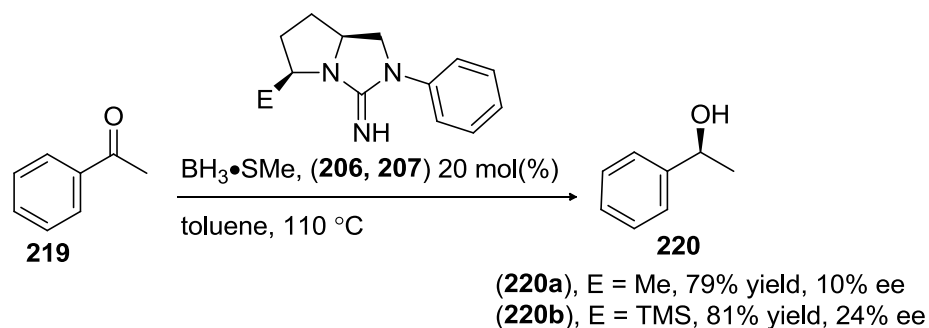
Scheme 64. Structure of the actual catalyst **97** in $\text{BH}_3\cdot\text{SMe}_2$ at room temperature or under reflux conditions.²⁹

To improve the enantioselectivity, the bulkier *N*-phenyl and *N*-methyl guanidines **205**, **206** and **207** were used in the reduction of phenacyl bromide (**Scheme 65**). The results indicated that only compound **207** gave any selectivity, with 8% ee (*S*-configuration), and all other products were obtained as racemates.



Scheme 65. Reduction of phenacyl bromide catalyzed by guanidines **205**, **206** and **207**.

Reduction of acetophenone **222** under identical conditions obtained (*S*)-**223b** in marginally better 24% ee for **212** and 10% ee for **211**. Both sets of experiments had to be performed in refluxing toluene as there was no observable reduction at room temperature (**Scheme 66**). It is clear from the reduction of **98** that the additional stereocentre at C5 is detrimental to the enantioselectivity of this process, possibly by virtue of a “mismatch” with the nature of chirality that is induced by the original stereogenic centre of *L*-proline. Additional support for this hypothesis would require synthesis of the *anti*-stereoisomers of **206** and **207**, which unfortunately are not accessible by the current synthetic method.

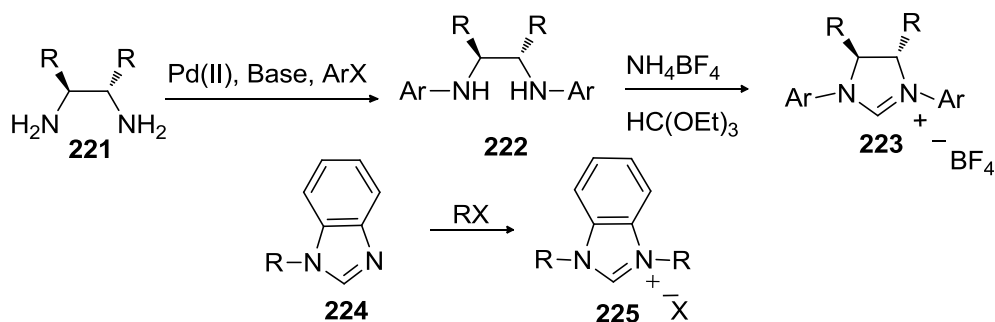


Scheme 66. Reduction of acetophenone catalyzed by guanidines **206** and **207**.

Research attempts were directed towards converting *N*-aryl urea **166** into *N*-heterocyclic carbenes for transition metal catalysis. The synthesis of these complexes is the topic of the next section.

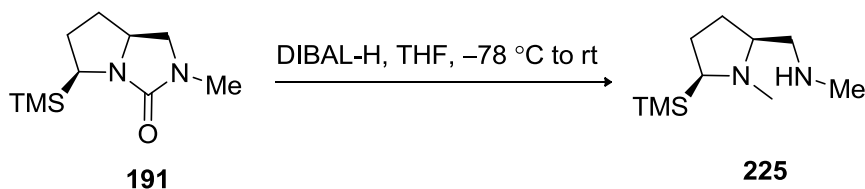
2.8. Synthesis of Metal *N*-Heterocyclic Carbene Complexes

There are not many examples of *N*-heterocyclic carbene complexes with annulated NHC ligands, most likely because they are unattainable from the common synthetic routes for these compounds. The most common way to synthesize these compounds is the *N*-alkylation and amination with aryl halides (Scheme 67).^{78,79}



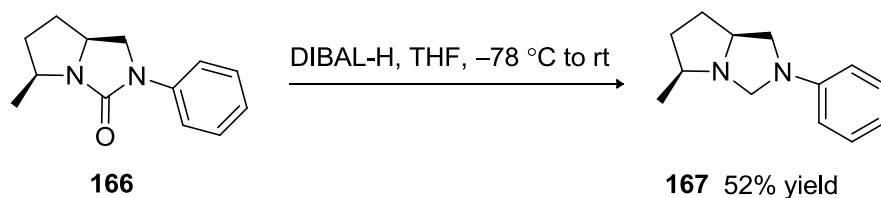
Scheme 67. *N*-Alkylation and amination of the appropriate aryl halides.^{73,74}

Synthesis of metal *N*-heterocyclic carbene complexes was started with reduction of **191** with DIBAL-H in THF at -78°C (Scheme 68). The result showed cleavage of the carbon-nitrogen bond instead of reduction of carbonyl group.



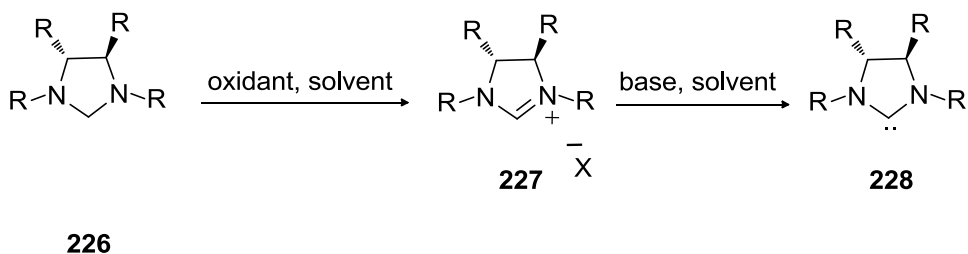
Scheme 68. Attempt to make amina.

Interestingly, reduction of compound **166** under identical conditions gave the desired product **167** in 52% yield (**Scheme 69**).



Scheme 69. Synthesis of ainal **167**.

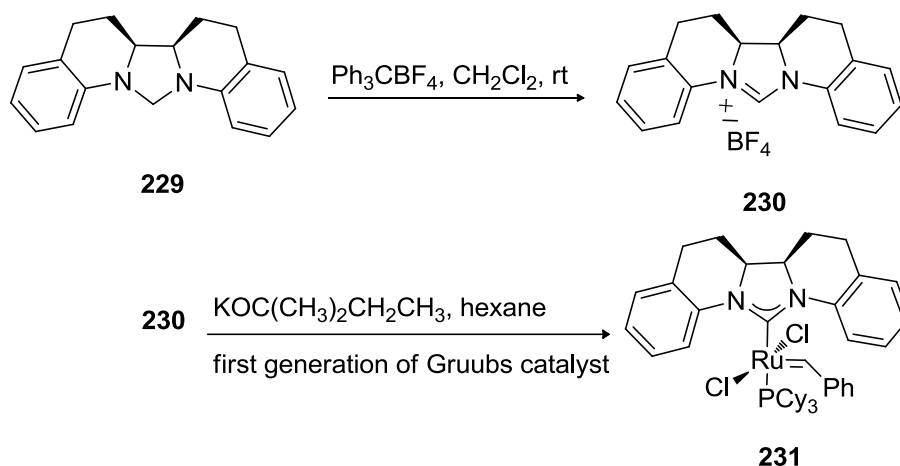
Oxidation of ainal, followed by addition of a base to the salt is the another way to make *N*-heterocyclic carbenes (**Scheme 70**).⁸⁰



Scheme 70. Synthesis of *N*-heterocyclic carbene by oxidation of ainal.

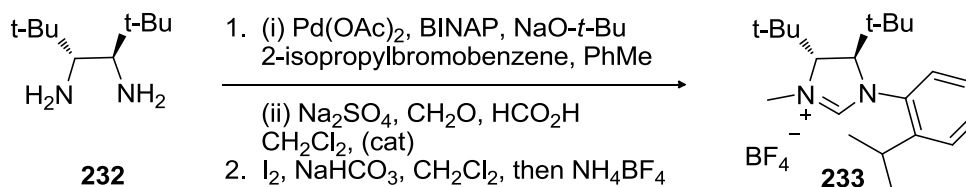
Iodine, triphenylcarbenium tetrafluoroborate and *N*-bromosuccinimide have been reported as oxidizing agents.^{75,81,82}

Blechert reported the synthesis of the imidazolium salt **230** by using tritylium tetrafluoroborate in the synthesis of ruthenium alkylidene complexes (**Scheme 71**).⁷⁵



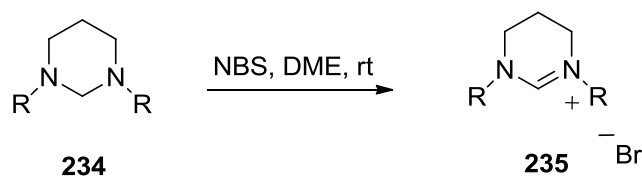
Scheme 71. Synthesis of imidazolinium salt **230** by using tritylium tetrafluoroborate by Blechert.⁷⁵

Collins and Fournier synthesized compound **233** by adding iodine and sodium bicarbonate in dichloromethane, followed by NH_4BF_4 addition (**Scheme 72**).⁷⁶



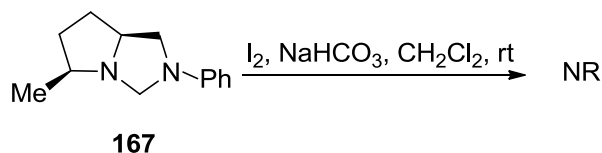
Scheme 72. Synthesis of compound **233** by using iodine and sodium bicarbonate in dichloromethane.⁷⁶

Buchmeiser indicated another method to oxidize aminals, using *N*-bromosuccinimide in DME to synthesize tetrahydropyrimidin-1-ium bromide **235** (**Scheme 73**).⁷⁷



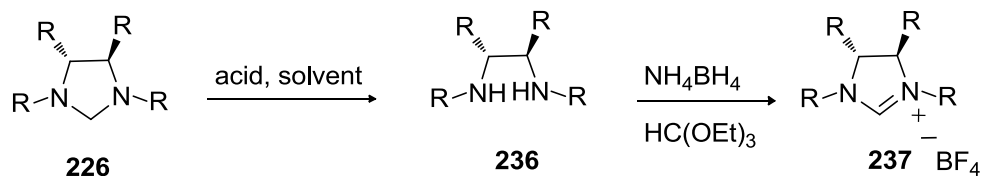
Scheme 73. Synthesis of tetrahydropyrimidin-1-ium bromide by using NBS.⁷⁷

Oxidation of aminor **167** by employing iodine and sodium bicarbonate was not successful and starting material was recovered (**Scheme 74**).

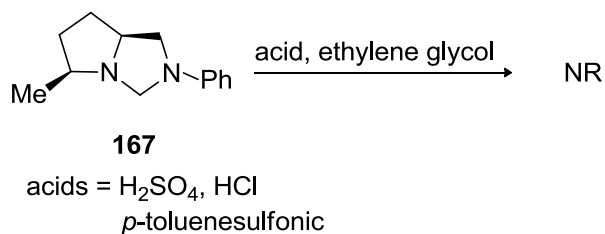


Scheme 74. Attempt of salt formation by using iodine.

We attempted to hydrolyze aminorals in order to determine the best method for the salt formation (**Scheme 75**). The synthesis of *N*-heterocyclic carbenes via hydrolyzing the aminor, followed by addition of triethyl orthoformate and ammonium tetrafluoroborate, failed in the first step. The aminor **167** was then screened with different acids in ethylene glycol under reflux, such as sulfuric acid and *p*-toluenesulfonic acid. However, the desired product was never made (**Scheme 76**).

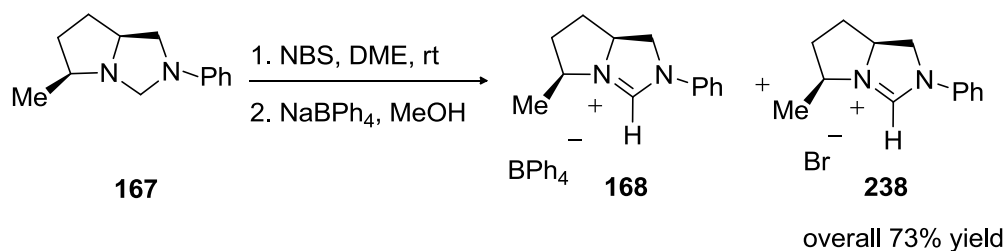


Scheme 75. Hydrolysis of aminor by using acid.



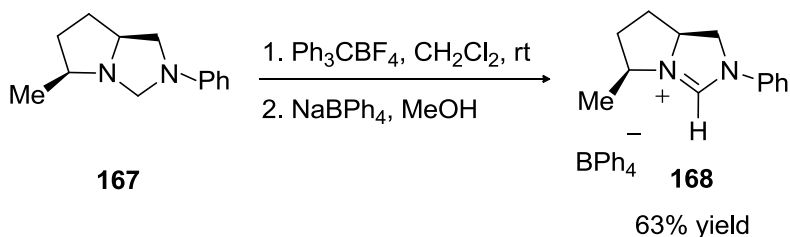
Scheme 76. Attempts to hydrolyze aminor by using different acids.

Imidazolinium salts **168** and **238** were generated by reaction of *N*-bromosuccinimide with aminal **166** in 1,2-dimethoxyethane (DME) followed by anion exchange with sodium tetraphenylborate in methanol in overall 73% yield (**Scheme 77**). Although this reaction gave good crude yield, it was not possible to purify the bromine salt.



Scheme 77. Synthesis of compound **168** and **238** by employing NBS.

The synthesis of pure **168** with triphenylcarbenium tetrafluoroborate in dichloromethane was performed in 63% yield (**Scheme 78**).

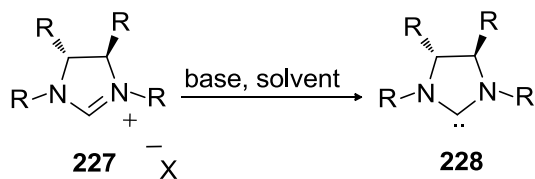


Scheme 78. Salt formation by using triphenylcarbenium tetrafluoroborate.

2.9. Synthesis of NHC complexes

As mentioned earlier in the Introduction in section 1.3, *N*-heterocyclic carbenes are generated by using a base. The appropriate choice of bases depends on the relative strength of the acid.

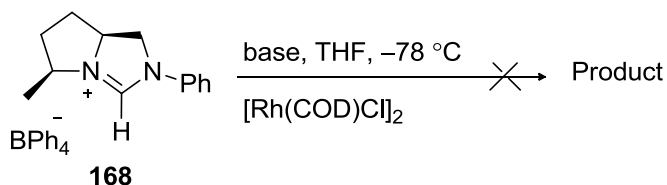
Several bases were applied in the synthesis of *N*-heterocyclic carbenes, such as *t*-BuOK, KHMDS, NaH, KOC(CH₃)₂CH₂CH₃ and organolithium species (such as *n*-BuLi, *s*-BuLi, *t*-BuLi or LDA) (**Scheme 79**).



bases = $\text{KOC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$,
 NaH , KHMDs , $t\text{-BuOK}$
 organolithium species

Scheme 79. Synthesis of *N*-heterocyclic carbenes.

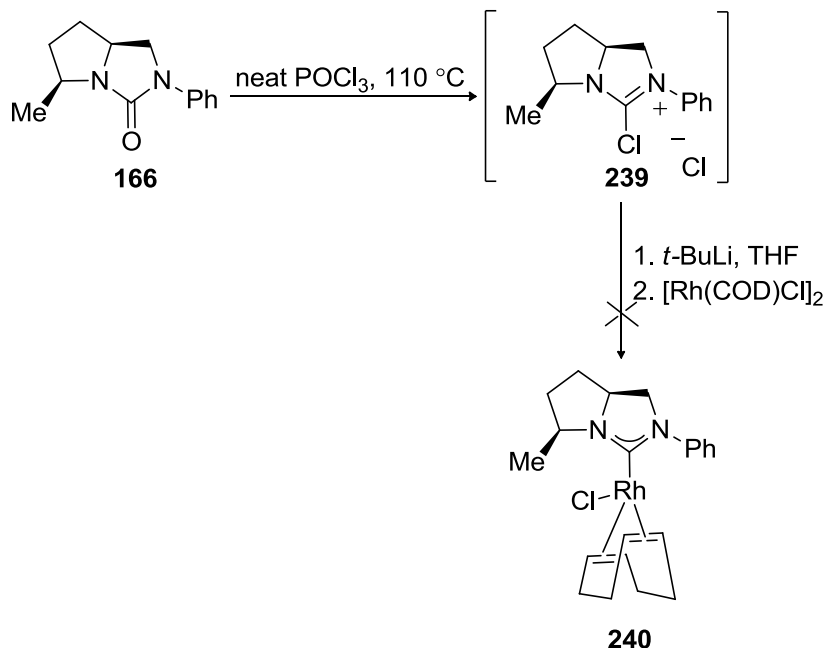
Compound **168** was treated with $t\text{-BuOK}$, the most common base in *N*-heterocyclic carbene formation, followed by addition of $[\text{Rh}(\text{COD})\text{Cl}]_2$. The result showed that no *N*-heterocyclic carbene was formed ($t\text{-BuOK}$, pK_a of the conjugate acid is around 17) (**Scheme 80**). When the imidazolium salt **168** was treated with potassium bis(trimethylsilyl)amide (pK_a of the conjugate acid is around 26), only the starting material was recovered. Probably, KHMDs is not strong enough to deprotonate the salt **168**. Attempts at deprotonation of **168** with organolithium species (pK_a of conjugate acid is ≤ 36), resulted in decomposition of the starting material.



bases = $\text{KOC}(\text{CH}_3)_2\text{CH}_2\text{CH}_3$,
 KHMDs , $t\text{-BuOK}$
 organolithium species

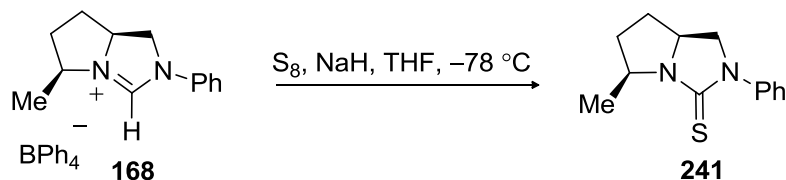
Scheme 80. Attempts to prepare complex by using different bases.

Another attempt to formation of *N*-heterocyclic carbene via using lithium bases failed, when lithium species were used after formation of chloroimidazolinium salt intermediate by using phosphoryl chloride (**Scheme 81**).



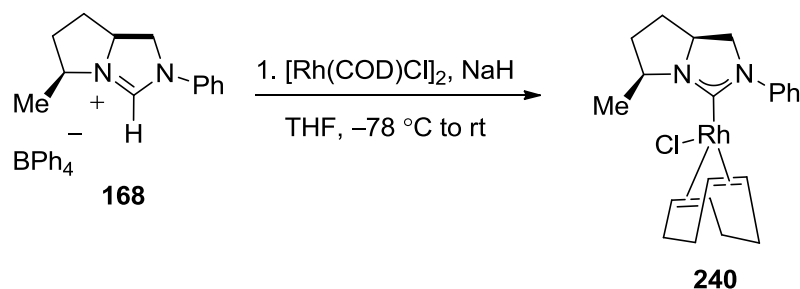
Scheme 81. Attempts to make carbene complex via chloroimidazolinium.

Generation of *N*-heterocyclic carbenes with sodium hydride (pK_a of conjugate acid is around 37) was successful. Thiourea **241** was obtained via successful generation of an *N*-heterocyclic carbene intermediate, followed by addition of S₈ in THF (**Scheme 82**).



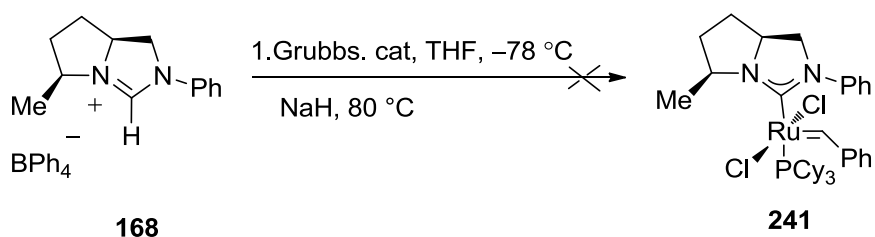
Scheme 82. Synthesis of thiourea via generation of an *N*-heterocyclic carbene.

Complex **240** was formed by addition of sodium hydride to a mixture of salt **168** and $[\text{Rh}(\text{COD})\text{Cl}]_2$ in THF. The result show that the desired chiral Rh–NHC complex as a mixture of coordination isomers in 58 % yield (**Scheme 83**).



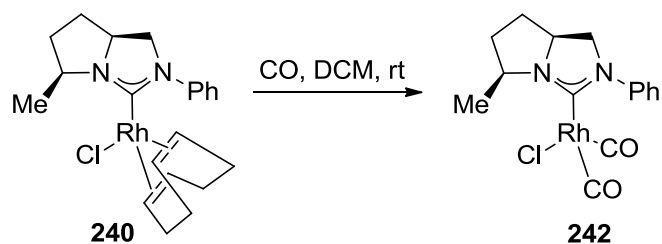
Scheme 83. Synthesis of complex **240** by using sodium hydride.

However, synthesis of a ruthenium *N*-heterocyclic carbene complex failed under this reaction condition maybe due to steric hindrance between substituents of NHC ligands and the alkylidene group or chloride of the ruthenium catalyst. The steric hindrance between adjacent groups can also lead to decrease of stability of the pentacoordinate NHC–Ru complexes (**Scheme 84**).



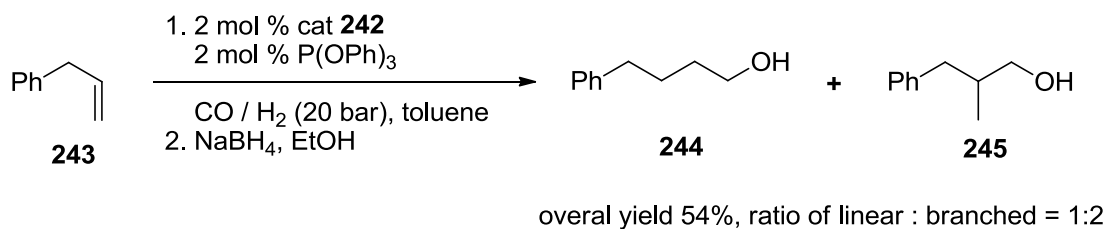
Scheme 84. Attempt to make ruthenium *N*-heterocyclic carbene complex.

Rh–NHC carbonyl complex **242** was synthesized in 78% yield as mixture of isomers in a roughly 10:1 ratio, by bubbling CO through a solution of **240** in methylene chloride for 3 h and stirring for 16 h under CO atmosphere (**Scheme 85**).



Scheme 85. Synthesis of complex **242**.

To establish the feasibility of its use as a catalyst in hydroformylation reactions, complex **242** was tested in the hydroformylation of allyl benzene with CO at 20 bar pressure, at 60 °C in the presence of triphenylphosphine as a ligand. Reduction with NaBH₄ gave the corresponding linear and branched alcohols in overall 54% yield in a ratio of 1:2, unfortunately no enantioselectivity was observed (**Scheme 86**).



Scheme 86. Hydroformylation of allyl benzene catalyzed by complex **242**.

3. Conclusions and Future Work

In summary, the *N*-protection of the imidazolinone **161** was done successfully by using TESCl without α -silyl carbanion formation. Different alpha to nitrogen substituted groups such as methyl, (diphenylhydroxy)methyl, allyl, silyl and stannyl derivatives were introduced diastereoselectively in *syn* fashion in yields ranging between 47% and 60%.

In contrast to the previously reported *N*-*t*-Bu derivatives, products **181-185** underwent smooth *N*-desilylation upon treatment with 2M aqueous HCl for 30 min at room temperature to give secondary ureas **186-190** in good yields (71-91%). The removal of the *N*-TES group from the product allowed the generation of new *N*-substituents. Transformation of ureas into guanidines and complexes was done by generation of imidazolinium salts via two different pathways and reagents. A number of Chloroimidazolinium salts were formed by using excess amounts of neat phosphoryl chloride and employed for guanidine formation. On the other hand, an imidazolinium salt was generated by reduction of urea by DIBAL-H, followed by oxidation by triphenylcarbenium tetrafluoroborate and finally, formation of *N*-heterocyclic carbene by employing sodium hydride to generate *N*-heterocyclic carbene complex.

Guanidines **206** and **207** were applied in borane-mediated asymmetric reduction of phenacyl bromide. A previous study by Basavaiah showed that *S*-configured alcohol product **99** in 83% ee.³⁰ Attempts to improve enantioselectivity of this reaction by using bulkier guanidines **207** gave 8% ee with *S*-configuration or as a racemate using **203**. Reduction of acetophenone under this conditions gave (*S*)-**220** in marginally better 24% ee for **207** and 10% for catalyst **206**. It is obvious from the reduction of phenacyl bromide that the additional stereocentre at C5 is detrimental to the enantioselectivity of this process. Higher selectivity probably could be achieved using *anti*-stereoisomers, which unfortunately are not accessible by this methodology.

The imidazolinium salt underwent complex formation by using sodium hydride at -78 °C to room temperature. This reaction gave a mixture of coordination isomers, after that Rh-NHC carbonyl complex

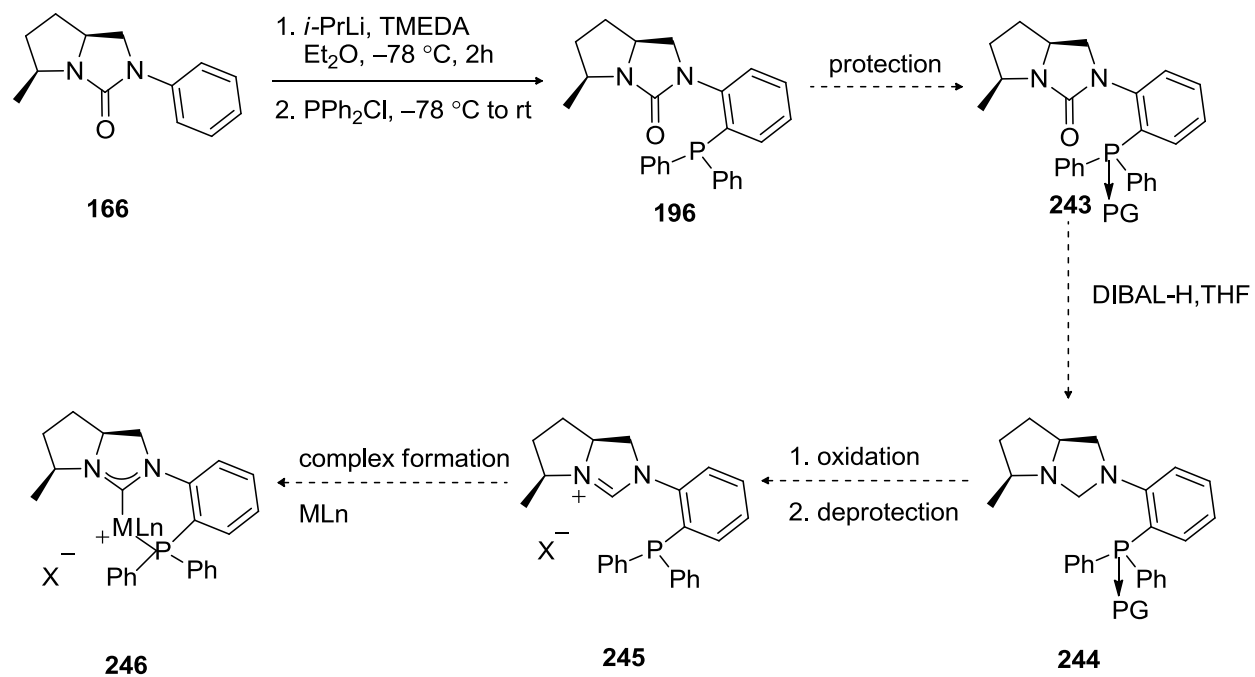
242 was synthesized smoothly by bubbling CO through a solution of **240** in methylene chloride, but NMR techniques showed presence of mixture of isomers. No enantioselectivity was observed when complex **242** was applied to hydroformylation of allylbenzene.

Future work will consider two different areas-modification of the ligand structure, and use of these ligands in different catalytic reactions, such as conjugate additions, hydrogenation or hydroformylation.

Further modifications on the ligand may include variation of the phenyl substituents, such as phosphorus derivatives with various electronic and steric properties. These properties can have direct effects on asymmetric induction in many catalytic organic reactions.

Although complex **242** did not give enantioselectivity in hydroformylation, this problem may be addressed by demanding synthesis of bidentate ligands, including phosphine as reported by Helmchen.⁶²

Product **246** can be prepared by lithiation of **166** followed by diphenylphosphine chloride quench to generate **196**, and then compound **196** can be protected by an appropriate protecting group such as borane to give compound **243**. Compound **243** may be reduced by DIBAL-H to generate **244**, which may convert to imidazolinium salt **245** after treatment with oxidizing agent. Subsequent deprotection of phosphorus, followed by *N*-heterocyclic carbene complex formation in presence of appropriate complex would provide **246** (Scheme 87).

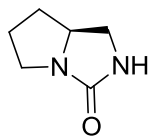


Scheme 87. Proposed synthetic route for a chiral bidentate complex **246**.

4. Experimental

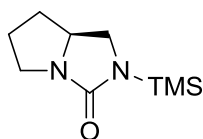
General. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Tetrahydrofuran (THF) was freshly dried and distilled over sodium/benzophenone ketyl under an atmosphere of nitrogen. Diethyl ether was distilled over LiAlH_4 and stored under an argon atmosphere. All alkyllithium bases were titrated against *N*-benzylbenzamide to a blue endpoint. All reactions were performed under argon in flame- or oven-dried glassware using syringe-septum cap techniques unless otherwise indicated. Column chromatography was performed on silica gel 60 (70-230 mesh). NMR spectra were obtained on a Bruker Avance 300 or 600 MHz instrument and are referenced to TMS or to the residual proton signal of the deuterated solvent for ^1H spectra, and to the carbon multiplet of the deuterated solvent for ^{13}C spectra according to known values. Enantiomeric ratios were determined on an Agilent 1100 series HPLC system at $\lambda = 254$ nm using a Chiralcel OD-H column, and were compared against racemic material. FT-IR spectra were obtained on an ATI Mattson Research Series spectrometer as KBr pellets for solids or on KBr discs for liquids. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. Mass spectra were obtained on an MSI/Kratos Concept 1S Mass Spectrometer. Melting points were determined on a Kofler hot-stage apparatus on recrystallized material unless otherwise indicated, and are uncorrected.

(-)-(S)-Tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (161).



A solution of *L*-proline hydantoin **173** (3.00 g, 0.02 mol) in THF (130 mL) was transferred by cannula into a stirred suspension of lithium aluminum hydride (2.45 g, 0.06 mol) in THF (130 mL) at 0 °C, and the mixture was thereafter allowed to stir at room temperature for 16 h. After cooling to 0 °C in an ice-water bath, workup was performed by sequential addition of water (2.5 mL), 15% aqueous NaOH solution (2.5 mL), and after 15 min, additional water (2.5 mL). The crude mixture containing aluminum salts was passed through a pad of Celite, rinsing with CH₂Cl₂. The organic phase was separated, dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure. Column chromatography (silica gel, 95:5 CH₂Cl₂:MeOH, R_f = 0.33) gave **161** as a colorless solid that was recrystallized from CH₂Cl₂ (1.52 g, 56%); mp 178-180 °C (CH₂Cl₂); [α]_D²⁰ -102.0 (c 0.50, CHCl₃); IR (KBr) ν_{max} 3264, 2955, 2886, 1693, 1481, 1433, 1404, 1313, 1260, 1193, 1091 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.47 (b, 1H), 3.78-3.71 (m, 1H), 3.65-3.53 (m, 2H) 3.32 (dd, 1H, *J* = 8.9, 2.4 Hz) 3.06-2.98 (m, 1H), 2.00-1.87 (m, 2H), 1.84-1.72 (m, 1H), 1.49-1.36 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 166.3, 59.4, 45.0, 42.9, 30.3, 25.1; EIMS [*m/z*(%)] 126 (M⁺, 7), 98 (67), 70 (35), 55 (100), 41 (34); HRMS (EI) calcd for C₆H₁₀N₂O: 126.0793; found: 126.0794.

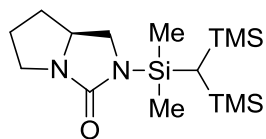
(-)-(S)-2-(Trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (177).



A solution of **161** (500 mg, 3.96 mmol) and TMEDA (0.71 mL, 4.75 mmol) in THF (20 mL) at 0 °C was treated with *i*-PrLi (6.10 mL, 0.8 M, 4.75 mmol), which was added dropwise over 15 min. After stirring for an additional 15 min, TMSCl (0.76 mL, 5.90 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water (20 mL), and extracted with CH₂Cl₂ (4 × 20 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.28) to give **174** as a colorless oil (310 mg, 46%); [α]_D²⁰ -53.7 (c 1.00, CHCl₃); IR (KBr, neat) ν_{max} 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162 cm⁻¹; ¹H NMR (300

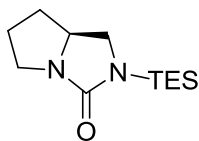
MHz, CDCl₃) δ 3.54-3.22 (m, 3H), 3.20 (dd, 1H, J = 7.8, 1.5 Hz), 3.03-2.95 (m, 1H), 1.94-1.75 (m, 3H), 1.33-1.26 (m, 1H), 0.24 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 167.5, 59.1, 45.8, 45.3, 30.6, 25.0, -1.2; EIMS [m/z (%)] 198 (M⁺, 8), 183 (100), 100 (29), 55 (62), HRMS (EI) calcd for C₉H₁₈N₂OSi: 198.1188; found:198.1190.

(-)-(S)-2-((Bis(trimethylsilyl)methyl)dimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (175).



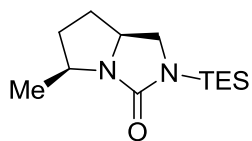
A solution of **174** (40 mg, 0.32 mmol) and TMEDA (0.10 mL, 0.67 mmol) in THF (4 mL) at -78 °C was treated with *i*-PrLi (0.60 mL, 1.1 M, 0.67 mmol). After 2 h, the reaction mixture was quenched with TMSCl (0.09 mL, 0.67 mmol) and, after 15 min, was stirred at room temperature for 16 h. After cooling in an ice-water bath, the reaction mixture was worked up by addition of water (7 mL) and extracted with CH₂Cl₂ (4 × 7 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.66) to give **175** as a colorless glass (29 mg, 26%); [α]_D²⁰ -26.9 (c 0.27, CHCl₃); IR (KBr) ν_{\max} 2955, 1675, 1481, 1397, 1319, 1256, 1010 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.69-3.53 (m, 3H), 3.21 (dd, 1H, J = 7.8, 1.6 Hz), 3.03-2.94 (m, 1H), 1.96-1.83 (m, 2H), 1.82-1.71 (m, 1H), 1.36-1.23 (m, 2H), 0.25 (d, 6H, J = 3.7 Hz), 0.1 (s, 18H); ¹³C NMR (75.5 MHz, CDCl₃) δ 167.5, 58.8, 46.1, 45.4, 30.8, 25.0, 2.9, 2.3, 1.7; EIMS [m/z (%)] 342 (M⁺, 88), 217 (62), 129 (73), 73 (100); HRMS (EI) calcd for C₁₅H₃₄N₂OSi₃: 342.1979; found: 342.1978.

(-)-(S)-2-(Triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (162**).**



A solution of **161** (800 mg, 6.34 mmol) and TMEDA (1.13 mL, 7.60 mmol) in THF (35 mL) at 0 °C was treated with *i*-PrLi (5.85 mL, 1.3 M, 7.60 mmol), added dropwise over 15 min. After stirring for an additional 15 min, chlorotriethylsilane (1.60 mL, 9.51 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water, and extracted with CH₂Cl₂ (4 × 30 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.54) to give **162** as a colorless oil (1.17 g, 77%); [α]_D²⁰ -46.2 (c 0.10, CHCl₃); IR (KBr, neat) ν_{max} 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162, 1007 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 3.74-3.59 (m, 3H), 3.25 (d, 1H, *J* = 7.8 Hz), 3.05-2.97 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.73 (m, 1H), 1.40-1.26 (m, 1H), 0.96 (t, 9H, *J* = 7.1 Hz), 0.77 (q, 6H, *J* = 7.1 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 167.9, 59.2, 46.4, 45.5, 30.6, 25.0, 6.9, 3.4; EIMS [*m/z*(%)] 240 (M⁺, 7), 211 (100), 100 (11); HRMS (EI) calcd for C₁₂H₂₄N₂Si: 240.1658; found: 240.1661.

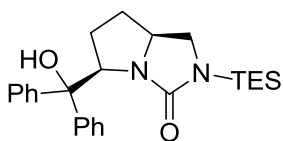
(-)-(5S,7aS)-5-Methyl-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (181**).**



A solution of **162** (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et₂O (30 mL) at -78 °C was treated with *i*-PrLi (1.92 mL, 1.30 M, 2.50 mmol). After 2 h, Me₂SO₄ (0.40 mL, 3.12 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL), and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.32) gave **181** as a colorless oil (315 mg, 60%); [α]_D²⁰ -24.4 (c 1.01, CHCl₃); IR (KBr, neat) ν_{max} 2954, 2875, 1678, 1460, 1400, 1266, 1132, 1006 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.01-3.96 (m, 1H), 3.69-3.57 (m, 1H), 3.49 (t, 1H, *J* = 8.9 Hz), 3.12 (dd, 1H, *J* = 7.1, 2.5 Hz), 2.16-2.13 (m, 1H), 1.92-1.81 (m, 1H), 1.75-1.70 (m, 1H), 1.62-1.49 (m, 1H), 1.39 (d, 3H, *J* = 6.4 Hz),

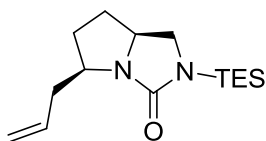
0.98 (t, 9H, $J = 7.5$ Hz), 0.82-0.75 (m, 6H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 163.9, 56.4, 46.3, 45.9, 38.5, 30.7, 24.9, 12.7, -2.5; EIMS [$m/z(\%)$] 254 (M^+ , 7), 25 (100), 211 (11), 100 (7); HRMS (EI) calcd for $\text{C}_{13}\text{H}_{26}\text{N}_2\text{OSi}$: 254.1814; found: 254.1821.

(+)-(5*R*,7*aS*)-5-(Hydroxydiphenylmethyl)-2-(triethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (182).



A solution of **162** (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et_2O (30 mL) at -78°C was treated with *i*-PrLi (1.56 mL, 1.6 M, 2.50 mmol). After 2 h, a solution of benzophenone (568 mg, 3.12 mmol) in THF (5 mL) was added slowly by cannula, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with CH_2Cl_2 (4×10 mL). The combined organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, $R_f = 0.62$) gave **182** as a colourless oil (495 mg, 56%); $[\alpha]_D^{20} +153.0$ (c 1.10, CHCl_3); IR (KBr, neat) ν_{max} 3206, 2954, 1647, 1414, 1262, 1145, 1006, 636, 600 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.64 (d, 2H, $J = 7.5$ Hz), 7.45 (d, 2H, $J = 7.5$ Hz), 7.34-7.16 (m, 6H), 4.32-4.26 (m, 1H), 3.90-3.85 (m, 1H), 3.63 (t, 1H, $J = 7.5$ Hz), 3.20 (dd, 1H, $J = 7.6, 3.1$ Hz), 2.17-2.04 (m, 1H), 1.97-1.83 (m, 1H), 1.58-1.45 (m, 1H), 1.42-1.30 (m, 2H), 0.94 (t, 9H, $J = 7.5$ Hz), 0.80-0.72 (m, 6H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 166.0, 147.7, 146.3, 128.2, 127.8, 127.7, 126.4, 126.3, 126.0, 76.8, 66.9, 60.7, 47.8, 29.2, 25.9, 6.8, 3.3; EIMS [$m/z(\%)$] 422 (M^+ , 21), 239 (25), 182 (53), 105 (92), 77 (100), 51 (64); HRMS (EI) calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_2\text{Si}$: 422.2390; found: 422.2384.

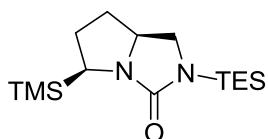
(+)-(5*R*,7*aS*)-5-Allyl-2-(triethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (183).



A solution of **162** (1.00 mg, 4.16 mmol) and TMEDA (0.74 mL, 5.00 mmol) in THF (30 mL) at $-78\text{ }^{\circ}\text{C}$ was treated with *i*-PrLi (3.84 mL, 1.3 M, 5.00 mmol).

After 2 h, a solution of CuCN (185 mg, 2.08 mmol) and LiCl (176 mg, 4.16 mmol) in THF (5 mL) was added slowly by cannula, and stirring was continued at $-78\text{ }^{\circ}\text{C}$. After 1 h, allyl bromide (0.43 mL, 4.50 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (30 mL) and extracted with CH_2Cl_2 ($4 \times 30\text{ mL}$). The combined organic extract was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.33$) gave **183** as a colorless oil (518 mg, 47%); $[\alpha]_D^{20} +10.2$ (c 0.75, CHCl_3); IR (KBr, neat) ν_{max} 2955, 1687, 1460, 1393, 1251, 1124, 1005 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 5.86-5.73 (m, 1H), 5.15-5.04 (m, 2H), 4.04-3.93 (m, 1H) 3.60-3.50 (m, 2H) 3.18 (dd, 1H, $J = 7.4, 2.1\text{ Hz}$), 3.04-2.96 (m, 1H), 2.44-2.33 (m, 1H), 2.14-2.00 (m, 1H), 1.94-1.85 (m, 2H), 1.56-1.45 (m, 1H), 0.98 (t, 9H, $J = 7.5\text{ Hz}$), 0.82-0.77 (m, 6H); ^{13}C NMR (75.5 MHz, CDCl_3); δ 163.0, 135.5, 117.1, 60.6, 56.0, 48.9, 35.2, 32.5, 29.9, 6.9, 3.5; EIMS [m/z (%)] 280 (M^+ , 4), 251 (30), 239 (100), 115 (36), 87 (53), 59 (35); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{28}\text{N}_2\text{OSi}$: 280.1971; found: 280.1974.

(-)-(5*S*,7*aS*)-2-(Triethylsilyl)-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (184).

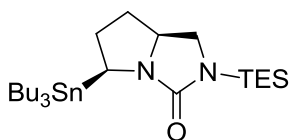


A solution of **162** (800 mg, 3.33 mmol) and TMEDA (0.60 mL, 4.00 mmol) in Et_2O (32 mL) at $-78\text{ }^{\circ}\text{C}$ was treated with *i*-PrLi (2.50 mL, 1.60 M, 4.00 mmol).

After 2 h, TMSCl (0.64 mL, 5.00 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath and worked up by addition of water (30 mL). After separation of the layers, the aqueous phase was extracted with CH_2Cl_2 ($4 \times 30\text{ mL}$), and the combined organic extract was dried over anhyd Na_2SO_4 , filtered and concentrated under reduced pressure. The product was purified by flash column

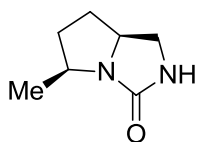
chromatography (silica gel, 9:1 hexane:EtOAc, R_f = 0.54) to give **184** as a colorless oil (893 mg, 86%); $[\alpha]_D^{20}$ -45.1 (c 0.59, CHCl_3); IR (KBr, neat) ν_{max} 2953, 1689, 1461, 1399, 1251, 1134, 1005 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 3.74-3.70 (m, 1H), 3.61 (t, 1H, J = 9.0 Hz), 3.18 (d, 1H, J = 9.6 Hz), 2.46 (t, 1H, J = 8.7 Hz), 2.02-1.97 (m, 1H), 1.92-1.86 (m, 1H), 1.71-1.66 (m, 1H), 1.49-1.45 (m, 1H), 0.96 (t, 9H, J = 7.8 Hz), 0.84-0.76 (m, 6H), 0.19 (s, 9H); ^{13}C NMR (150.9 MHz, CDCl_3) δ 166.1, 60.5, 49.7, 47.7, 31.6, 27.9, 6.8, 3.4, -1.0; EIMS [m/z (%)] 312 (M^+ , 12), 297 (100), 283 (70), 239 (58), 87 (36), 73 (32), 59 (40); HRMS (EI) calcd for $\text{C}_{15}\text{H}_{32}\text{N}_2\text{OSi}_2$: 312.2053; found: 312.2045.

(-)-(5*S*,7*aS*)-2-(Tributylstannyl)-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (185).



A solution of **162** (207 mg, 0.86 mmol) and TMEDA (0.15 mL, 1.03 mmol) in Et_2O (10 mL) at -78°C was treated with *i*-PrLi (0.65 mL, 1.6 M, 1.03 mmol). After 2 h, Bu_3SnCl (0.35 mL, 1.29 mmol) was added, and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with Et_2O (4×10 mL). The combined organic extract was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.92) gave **185** as a colorless oil (358 mg, 60%); $[\alpha]_D^{20}$ -17.8 (c 0.59, CHCl_3); IR (KBr, neat) ν_{max} 2954, 1674, 1462, 1401, 1257, 1204, 1123, 1005 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 3.69-3.63 (m, 1H), 3.59 (t, 1H, J = 9.0 Hz), 3.18 (dd, 1H, J = 7.4, 1.6 Hz), 2.69 (t, 1H, J = 8.3 Hz), 2.07-1.92 (m, 2H), 1.83-1.73 (m, 1H), 1.58-1.46 (m, 6H), 1.39-1.26 (m, 7H), 0.99-0.74 (m, 24H), 0.81-0.74 (m, 6H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 167.5, 59.7, 46.6, 44.9, 31.6, 29.7, 29.3, 27.6, 13.8, 11.4, 6.8, 3.4; EIMS [m/z (%)] 473 ($\text{M}-\text{C}_4\text{H}_9$, 71), 239 (32), 209 (69), 41 (100); HRMS (EI) calcd for $\text{C}_{20}\text{H}_{41}\text{N}_2\text{OSiSn}$: 473.2010; found: 473.2006.

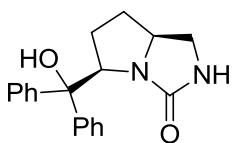
(–)-(5*S*,7*aS*)-5-Methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (186**).**



A solution of **181** (333 mg, 1.32 mmol) in MeOH (1.3 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL).

The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.10) gave **186** as a colorless solid (155 mg, 84%) that was recrystallized from EtOAc/hexane; mp 65–67 °C (EtOAc/hexane); [α]_D²⁰ –20.9 (c 1.00, CHCl₃); IR (KBr, neat) ν_{max} 3298, 2968, 1697, 1487, 1440, 1271, 1155, 1125, 1093 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 4.77 (b, 1H), 4.13–4.03 (m, 1H), 3.74–3.68 (m, 1H), 3.58 (t, 1H, *J* = 8.5 Hz), 3.24 (t, 1H, *J* = 8.2 Hz), 2.26–2.13 (m, 1H), 2.01–1.92 (m, 1H), 1.79–1.69 (m, 1H), 1.67–1.56 (m, 1H), 1.43 (d, 3H, *J* = 6.8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 162.0, 60.9, 51.8, 46.0, 35.8, 29.5, 18.3; EIMS [*m/z*(%)] 140 (M⁺, 26), 125 (100), 69 (71). HRMS (EI) calcd for C₇H₁₂N₂O: 140.0950; found: 140.0947.

(+)-(5*R*,7*aS*)-5-(Hydroxydiphenylmethyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (187**).**

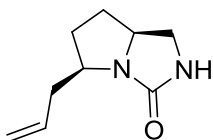


A solution of **182** (100 mg, 0.24 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (4 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10

mL). The crude mixture was extracted with CH₂Cl₂ (4 × 7 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.19) gave **187** as a colorless oil (58 mg, 80%); [α]_D²⁰ +146.0 (c 0.65, CHCl₃); IR (KBr, neat) ν_{max} 3206, 2955, 1668, 1487, 1448, 1416, 1266, 1150, 1005 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 2H, *J* = 7.5 Hz), 7.47 (d, 2H, *J* = 7.5 Hz), 7.34–7.17 (m, 6H), 5.34 (b, 1H), 4.30–4.24 (m, 1H), 3.95–3.92 (m, 1H), 3.56 (t, 1H, *J* = 8.4 Hz), 3.20 (dd, 1H, *J* = 8.4, 1.8 Hz), 2.17–2.03 (m, 2H), 2.00–1.88 (m, 1H), 1.66–1.60 (m, 1H), 1.36–1.29 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 163.6, 147.5, 145.9, 127.9, 127.8, 126.6, 126.5, 126.4, 125.8, 77.2, 66.6, 60.6, 44.0, 28.9, 25.7;

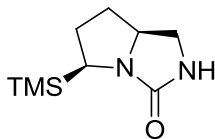
EIMS [$m/z(\%)$] 308 (M^+ , 17), 182 (44), 125 (68) 105 (100), 77 (40); HRMS (EI) calcd for $C_{19}H_{20}N_2O_2$: 308.1525; found: 308.1529.

(–)-(5*R*,7*aS*)-5-Allyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (188).



A solution of **183** (238 mg, 0.89 mmol) in MeOH (1.2 mL) was treated with 2 M aq. HCl (6 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous $NaHCO_3$ (10 mL). The crude mixture was extracted with CH_2Cl_2 (4×10 mL), and the combined organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.11$) gave **188** as a colorless oil (111 mg, 82%); $[\alpha]_D^{20} -5.3$ (c 1.01, $CHCl_3$); IR (KBr) ν_{max} 3229, 2968, 1682, 1490, 1451, 1404, 1281, 1145, 1004 cm^{-1} ; 1H NMR (300 MHz, $CDCl_3$) δ 5.84-5.72 (m, 1H), 5.18-5.04 (m, 2H), 4.13-4.02 (m, 2H), 3.63-3.54 (m, 2H), 3.23 (t, 1H, $J = 8.0$ Hz), 3.08-3.00 (m, 1H), 2.36-2.26 (m, 1H), 2.16-2.03 (m, 1H), 1.97-1.90 (m, 2H), 1.65-1.52 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.4, 135.3, 117.4, 60.8, 55.4, 46.1, 35.4, 32.4, 29.3; EIMS [$m/z(\%)$] 166 (M^+ , 3), 125 (100); HRMS (EI) calcd for $C_9H_{14}N_2O$: 166.1106; found: 166.1105.

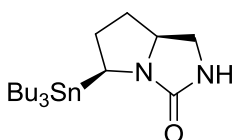
(–)-(5*S*,7*aS*)-5-(Trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (189).



A solution of **184** (413 mg, 1.32 mmol) in MeOH (1.8 mL) was treated with 2 M aq. HCl (10 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous $NaHCO_3$ (10 mL). The crude mixture was extracted with CH_2Cl_2 (4×10 mL), and the combined organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.13$) gave **189** as a colorless solid (238 mg, 91%) that was recrystallized from EtOAc/hexane; mp 100-103 °C (EtOAc/hexane); $[\alpha]_D^{20} -67.1$ (c 0.52,

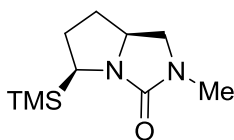
CHCl₃); IR (KBr) ν_{\max} 3259, 2948, 1682, 1490, 1446, 1411, 1272, 1243, 1126 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.40 (b, 1H), 3.92-3.81 (m, 1H), 3.65 (t, 1H, J = 8.5 Hz), 3.26 (dd, 1H, J = 8.7, 3.4 Hz), 2.47 (dd, 1H, J = 7.8, 2.4 Hz), 2.12-1.88 (m, 2H), 1.79-1.52 (m, 2H), 0.18 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 164.1, 60.6, 49.2, 44.0, 31.2, 27.9, -1.1; EIMS [m/z (%)] 199 (M⁺, 37) 183 (100), 73 (36); HRMS (FAB) calcd for C₉H₁₈N₂OSi: 199.1267; found: 199.1266.

(-)-(5*S*,7*aS*)-5-(Tributylstannyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (190).



A solution of **185** (240 mg, 0.58 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.17) gave **190** as a colorless oil (141 mg, 71%); [α]_D²⁰ -16.5 (c 0.40, CHCl₃); IR (KBr, neat) ν_{\max} 3229, 2954, 1692, 1453, 1265, 1072 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.47 (b, 1H), 3.82-3.75 (m, 1H), 3.63 (t, 1H, J = 8.0 Hz), 3.24 (dd, 1H, J = 8.7, 2.4 Hz), 2.67 (t, 1H, J = 8.5 Hz), 2.07-1.98 (m, 2H), 1.84-1.74 (m, 1H), 1.55-1.47 (m, 6H), 1.36-1.29 (m, 7H), 0.93-0.88 (m, 15H); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.8, 59.7, 44.4, 43.3, 31.5, 29.7, 29.3, 27.3, 13.8, 11.2; EIMS [m/z (%)] 359 (M-C₄H₉, 68), 125 (73), 68 (56), 41 (100); HRMS (EI) calcd for C₁₄H₂₇N₂OSn: 359.1145; found: 359.1149.

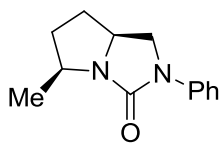
(5*S*,7*aS*)-2-Methyl-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (191).



A solution of **189** (270 mg, 1.36 mmol) in DMF (5 mL) at 0 °C was transferred by cannula into a stirred suspension of sodium hydride (131 mg, 5.46 mmol) in DMF (5 mL) at 0 °C. After 45 min iodomethane (0.24 mL, 3.82 mmol) was added into mixture at 0 °C, the mixture was thereafter allowed to stir to at room temperature for 16 h. After cooling

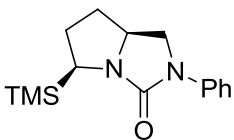
to 0 °C in an ice-water bath, workup was performed by sequential addition of NH₄Cl (20 mL) and water (80 mL), and the mixture was extracted with CH₂Cl₂ (4 × 10 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.51) gave **191** as a colourless oil (171 mg, 60%); [α]_D²⁰ +10.0 (c 0.75, CHCl₃); IR (KBr) ν_{max} 2955, 1687, 1460, 1393, 1251, 1124, 1005, 961, 740 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 3.69-3.60 (m, 1H), 3.47 (t, 1H), 3.18 (dd, 1H, *J* = 6.7, 2.5 Hz), 2.76 (s, 3H) 2.43 (dd, 1H, *J* = 7.7, 2.9 Hz), 2.09-1.97 (m, 1H), 1.92-1.81 (m, 1H), 1.71-1.58 (m, 1H), 1.57-1.43 (m, 1H), 0.17 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃): δ 162.7, 57.4, 50.8, 50.1, 31.4, 31.01, 27.6; EIMS [*m/z*(%)] 213 (M⁺, 6.3), 197 (100), 139 (28.2), 73 (25.7). HRMS (EI) calcd for C₁₀H₂₀N₂OSi: 212.1345; found: 212.1349.

(–)-(5*S*,7*aS*)-5-Methyl-2-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (166).



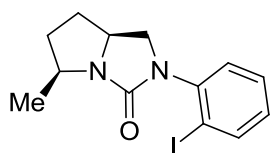
A 2-necked flask under argon was charged with **186** (643 mg, 4.59 mmol), CuI (700 mg, 3.67 mmol), TMEDA (0.09 mL, 0.90 mmol), iodobenzene (1.13 mL, 10.12 mmol), K₂CO₃ (1671 mg, 12.20 mmol), and toluene (6 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH₂Cl₂ (50 mL), filtered through Celite and washed with additional CH₂Cl₂ (4 × 30 mL). The organic filtrate was washed with H₂O (4 × 50 mL), dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, R_f = 0.18) gave **166** as a colorless solid (738 mg, 74%) that was recrystallized from EtOAc/hexane; mp 110-112 °C (EtOAc/hexane); [α]_D²⁰ –22.5 (c 0.90, CHCl₃); IR (KBr) ν_{max} 2890, 1943, 1862, 1681, 1598, 1384, 1280, 1153, 1085, 1054 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.51-7.48 (m, 2H), 7.36-7.28 (m, 2H), 7.04-6.99 (m, 1H), 4.09-4.01 (m, 1H), 3.91 (t, 1H, *J* = 8.4 Hz), 3.87-3.82 (m, 1H), 3.69 (t, 1H, *J* = 8.4 Hz), 2.25-2.19 (m, 1H), 2.14-2.07 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.64 (m, 1H), 1.44 (d, 3H, *J* = 6.3 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 156.7, 140.7, 128.7, 122.04, 117.3, 56.6, 52.2, 50.7 35.6, 29.9, 18.4; EIMS [*m/z*(%)] 217 (M⁺, 14), 201 (74), 69 (100), 55 (49); HRMS (EI) calcd for C₁₃H₁₆N₂O: 216.1263; found: 216.1262.

(–)-(5*S*,7*aS*)-2-Phenyl-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (194).



A 2-necked flask under argon was charged with **189** (100 mg, 0.51 mmol), CuI (77 mg, 0.40 mmol), TMEDA (0.01 mL, 0.10 mmol), iodobenzene (0.12 mL, 1.10 mmol), K₂CO₃ (138 mg, 1.00 mmol), and toluene (1 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH₂Cl₂ (15 mL), filtered through Celite and washed with additional CH₂Cl₂ (4 × 15 mL). The organic filtrate was washed with H₂O (4 × 15 mL), dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, R_f = 0.41) gave **194** as a colorless solid (56 mg, 40%) that was recrystallized from EtOAc/hexane; mp 138–140 °C (EtOAc/hexane); [α]_D²⁰ –70.1 (c 1.50, CHCl₃); IR (KBr) ν_{max} 3396, 2917, 1704, 1600, 1502, 1481, 1402, 1317, 1243, 1153, 1128, 1076, 1027 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.57 (dd, 2H, *J* = 7.8, 1.3 Hz), 7.54–7.39 (m, 2H), 7.03 (t, 1H, *J* = 7.3 Hz), 4.03–4.00 (t, 1H, *J* = 8.9 Hz), 3.88–3.79 (m, 1H), 3.66 (dd, 1H, *J* = 9.0, 3.3 Hz), 2.56 (dd, 1H, *J* = 10.2, 7.8 Hz), 2.19–2.10 (m, 1H), 1.92–1.84 (m, 1H), 1.80–1.71 (m, 1H), 1.64–1.60 (m, 1H), 0.23 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 159.2, 140.6, 128.8, 122.4, 117.7, 56.5, 49.8, 48.9, 31.8, 27.9, –0.99; EIMS [*m/z*(%)] 274 (M⁺, 11), 259 (81), 183 (76), 73 (100); HRMS (EI) calcd for C₁₅H₂₂N₂OSi: 274.1501; found: 274.1491.

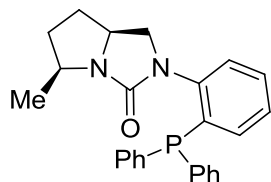
(5*S*,7*aS*)-2-(2-Iodophenyl)-5-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (195).



A solution of **166** (100 mg, 0.46 mmol) and TMEDA (0.08 mL, 0.55 mmol) in THF (4 mL) at –78 °C was treated with *i*-PrLi (0.44 mL, 1.2 M, 0.55 mmol). After 2 h, a solution of 1,2-diiodoethane (197 mg, 0.70 mmol) in THF (2 mL) was added slowly by cannula, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R_f = 0.23) gave **195** as a colorless solid (106 mg, 67%) that was recrystallized from EtOAc/hexane; mp 144–

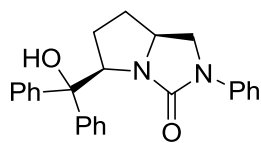
147 °C (EtOAc/hexane); $[\alpha]_{\text{D}}^{20}$ -29.5 (c 2.50, CHCl₃); IR (KBr) ν_{max} 3072, 2987, 2955, 2887, 2839, 1685, 1565, 1468, 1440, 1397, 1280, 1103, 1019, 949, 862, 759, 717, 678, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.86 (dd, 1H, J = 7.2, 1.4 Hz), 7.40-7.34 (m, 1H), 7.30 (dd, 1H, J = 6.5, 1.4 Hz), 7.00 (dd, 1H, J = 6.1, 1.8 Hz), 4.13-4.05 (m, 1H), 3.85-3.77 (m, 2H), 3.70-3.66 (m, 1H), 2.26-2.14 (m, 1H), 2.08-2.00 (m, 1H), 1.85-1.71 (m, 2H), 1.50 (d, 3H, J = 6.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.1, 141.9, 139.7, 129.3, 129.1, 128.9, 99.2, 57.9, 52.9, 52.4, 35.4, 29.7, 18.4; HRMS (EI) calcd for C₁₃H₁₅N₂O: 342.0221; found: 342.0218.

(5*S*,7*aS*)-2-(2-(Diphenylphosphino)phenyl)-5-methyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (196).



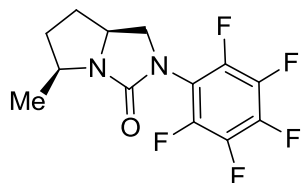
A solution of **166** (100 mg, 0.46 mmol) and TMEDA (0.08 mL, 0.55 mmol) in THF (4 mL) at -78 °C was treated with *i*-PrLi (0.44 mL, 1.2 M, 0.55 mmol). After 2 h, PPh₂Cl (0.12 mL, 0.70 mmol) was added, and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath and quenched with a saturated solution of NH₄Cl (4 mL), worked up with water (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane : EtOAc, R_f = 0.21) gave **196** as a colorless oil (85 mg, 47%); $[\alpha]_{\text{D}}^{20}$ +15.9 (c 1.00, CHCl₃); IR (KBr, neat) ν_{max} 3054, 2966, 1691, 1584, 1471, 1435, 1347, 1217, 741, 694, 663, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.83-7.64 (m, 2H), 7.34-7.32 (m, 10H), 7.20-7.15 (m, 1H), 6.89-6.85 (m, 1H), 3.88-3.80 (m, 1H), 3.70-3.61 (m, 2H), 3.60 (t, 1H, J = 8.3 Hz), 2.10-1.99 (m, 1H), 1.93-1.85 (m, 1H), 1.56-1.51 (m, 2H), 1.28 (d, 3H, J = 6.8 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.9, 143.7 (d, J = 20.8 Hz), 137.1 (d, J = 13.6 Hz), 136.5 (d, J = 10.5 Hz), 134.2, 134.1, 134.0, 133.9, 133.7, 130.1, 128.8, 128.5, 128.4, 128.0, 127.4, 57.8, 53.3, 52.8, 35.1, 29.5, 18.0; HRMS (EI) calcd for C₂₅H₂₅N₂OP: 400.1699; found: 400.1701.

(5*R*,7*aS*)-5-(Hydroxydiphenylmethyl)-2-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (197).



A 2-necked flask under argon was charged with **187** (500 mg, 1.62 mmol), CuI (247 mg, 1.30 mmol), TMEDA (0.1 mL, 0.65 mmol), iodobenzene (0.4 mL, 3.56 mmol), K₂CO₃ (560 mg, 4.05 mmol), and toluene (3mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CH₂Cl₂ (15 mL), filtered through Celite and washed with additional CH₂Cl₂ (4 × 15 mL). The organic filtrate was washed with H₂O (4 × 15 mL), dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, R_f = 0.41) gave **197** as a colorless solid (303 mg, 49%) that was recrystallized from EtOAc/hexane; mp 195-198 °C (EtOAc/hexane); [α]_D²⁰ -153.8 (c 1.15, CHCl₃); IR (KBr) ν_{max} 3216, 3059, 3024, 2954, 2918, 1655, 1598, 1500, 1451, 1384, 1268, 1170, 965, 725, 692 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73 (d, 2H, *J* = 7.8 Hz), 7.51-7.47 (m, 4H), 7.37-7.17 (m, 8H), 7.07 (t, 1H, *J* = 7.4 Hz), 4.44-4.40 (dd, 1H, *J* = 7.1, 1.7 Hz), 4.03-3.37 (m, 3H), 3.67 (dd, 1H, *J* = 7.0, 2.0 Hz), 2.30-2.16 (m, 1H), 2.12-2.00 (m, 1H), 1.72-1.59 (m, 1H), 1.47-1.36 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 159.9, 148.0, 146.4, 140.2, 129.3, 128.5, 128.4, 127.2, 127.0, 126.9, 126.4, 123.8, 119.1, 77.2, 68.0, 57.0, 49.4, 30.0, 26.2; HRMS (EI) calcd for C₂₅H₂₄N₂O₂: 384.1847; found: 384.1838.

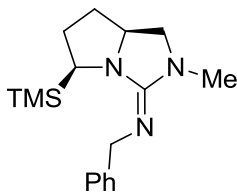
(5*S*,7*aS*)-5-Methyl-2-(perfluorophenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-one (199).



A solution of **186** (200 mg, 1.43 mmol) in DMF (5 mL) at 0 °C was transferred by cannula into a stirred suspension of sodium hydride (68 mg, 2.87 mmol) in DMF (5 mL) at 0 °C, after 45 min hexafluorobenzene (0.17 mL, 1.44 mmol) was added into mixture at 0 °C, the mixture was thereafter allowed to stir to at room temperature for 16 h. After cooling to 0 °C in an ice-water bath, workup was performed by sequential addition of NH₄Cl (20 mL) and water (80 mL), and extracted with CH₂Cl₂ (4 × 10 mL). The combined

organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane : EtOAc, $R_f = 0.59$) gave **199** as a colourless oil (212 mg, 48%); $[\alpha]_D^{20} - 56.1$ (c 3.5, CHCl_3); IR (KBr) ν_{max} 2944, 2877, 1706, 1651, 1505, 1397, 1308, 1168, 982, 748 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 4.24-4.14 (m, 1H), 3.85-3.76 (m, 2H), 3.65 (t, 1H, $J = 8.3$ Hz), 2.82-2.20 (m, 1H), 2.12-2.03 (m, 1H), 1.88-1.79 (m, 1H), 1.75-1.65 (m, 1H), 1.43 (d, 3H, $J = 7.12$ Hz); ^{13}C NMR (75.5 MHz, CDCl_3): δ 156.4, 144.1 (d, $^1J^{13}\text{C}-^{19}\text{F} = 251.3$ Hz), 140.1 (d, $^1J^{13}\text{C}-^{19}\text{F} = 253.8$ Hz), 137.9 (d, $^1J^{13}\text{C}-^{19}\text{F} = 251.3$ Hz), 114.9-114.5 (m), 58.6, 52.2, 35.5, 29.6, 29.6, 18.1; ^{19}F NMR (282.4 MHz, CDCl_3): -144.9, -156.8, -162.5; HRMS (EI) calcd for $\text{C}_{13}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$: 306.0789; found: 306.0792.

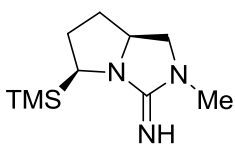
(Z)-N-((5S,7aS)-2-Methyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-ylidene)-1-phenylmethanamine (202).



A solution of **191** (119 mL, 0.56 mmol) in POCl_3 (0.5 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl_3 was removed by under reduced pressure. The crude intermediate was dissolved in MeCN (0.5 mL) and transferred to a solution of benzylamine (0.07 mL, 0.67 mmol) and triethylamine (0.16 mL, 1.12 mmol) in MeCN (0.5 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH_2Cl_2 (3×10 mL). After evaporation of the combined organic extract, the residue was dissolved in water (15 mL) and washed with toluene (3×10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH_2Cl_2 (4×15 mL). The combined organic extract was dried over anhyd. Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **202** as a colorless oil (57 mg, 35%); $[\alpha]_D^{20} + 54.6$ (c 0.6, CHCl_3); IR (KBr, neat) ν_{max} 2955, 1675, 1481, 1397, 1319, 1256, 1010, 889 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.28 (dd, 4H, $J = 7.8, 6.6$ Hz), 7.15 (t, 1H, $J = 6.18$ Hz), 4.58 (d, 1H, $J = 15.5$ Hz), 4.39 (d, 1H, $J = 15.5$ Hz), 3.76 (s, 1H), 3.33 (t, 1H, $J = 8.7$ Hz), 3.17 (dd, 1H, J

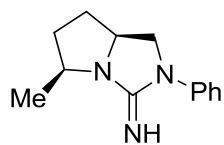
= 5.5, 3.6 Hz), 2.76 (s, 4H), 2.09-1.93 (m, 2H), 1.83 (s, 1H), 1.54-1.41 (m, 1H), 0.06 (s, 9H); ^{13}C NMR (75.5 MHz, DMSO- d_6); δ 157.4, 143.9, 128.1, 127.5, 126.0, 59.7, 56.2, 52.1, 51.2, 40.8, 30.8, 29.5, 0.38; EIMS [$m/z(\%)$] 302 (M^+ , 2), 228 (40), 91(100). HRMS (EI) calcd for $\text{C}_{17}\text{H}_{27}\text{N}_3\text{Si}$: 301.1974; found: 301.1982.

(5*S*,7*aS*)-2-Methyl-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-imine (205).



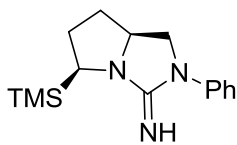
A solution of **191** (10 mg, 0.47 mmol) in POCl_3 (0.5 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl_3 was removed under reduced pressure. The crude intermediate was dissolved in MeCN (0.5 mL) and transferred to a solution of aqueous ammonia (0.18 mL, 4.57 mmol) and triethylamine (2.55 mL, 18.00 mmol) in MeCN (0.5 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH_2Cl_2 (3×10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3×10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH_2Cl_2 (4×15 mL). The combined organic extract was dried over anhyd. Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **205** as colorless oil (29 mg, 30%) $[\alpha]_{\text{D}}^{20} -18.6$ (c 0.35, CHCl_3); IR (KBr, neat) ν_{max} 3428, 2946, 1641, 1490, 1407, 1301, 1024, 973, 904, 840, 755, 593 cm^{-1} ; ^1H NMR (300 MHz, acetone- d_6): δ 3.62-3.55 (m, 1H), 3.39 (dd, 1H, $J = 7.26, 1.5$ Hz), 3.12 (dd, 1H, $J = 3.3, 2.7$ Hz), 2.90 (s, 1H), 2.65 (s, 3H), 2.46-2.4 (m, 1H), 1.86-1.81 (m, 2H), 1.60-1.42 (m, 2H), 0.15 (s, 9H); ^{13}C NMR (75.5 MHz, acetone- d_6); δ 163.1, 59.4, 53.8, 52.0, 32.8, 30.9, 28.5, -0.3 ; EIMS [$m/z(\%)$] 212 (M^+ , 4.8), 196 (100), 138 (62), 73 (35). HRMS (EI) calcd for $\text{C}_{10}\text{H}_{21}\text{N}_3\text{Si}$: 211.1505; found: 211.1493.

(5*S*,7*aS*)-5-Methyl-2-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-imine (206).



A solution of **166** (218 mg, 1.02 mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.53 mL, 10.00 mmol) and triethylamine (6.75 mL, 40.0 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield **206** as colorless oil (82 mg, 41%) [α]_D²⁰ –49.0 (c 0.35, CHCl₃); IR (KBr, neat) ν_{max} 3457, 2919, 2057, 1629, 1500, 1153, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.35 (m, 4H) 7.10-7.05 (m, 1H), 4.17-4.05 (m, 1H), 4.05-3.95 (m, 1H), 3.84 (t, 2H, *J* = 8.8 Hz), 3.65 (t, 1H, *J* = 8.5 Hz), 2.31-2.18 (m, 1H), 2.13-2.04 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.60 (m, 1H), 1.44 (d, 3H, *J* = 6.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 156.4, 141.0, 129.2, 123.1, 120.1, 58.6, 55.2, 52.1, 36.2, 28.7, 18.0; EIMS [*m/z*(%)] 215 (M⁺, 6), 160 (100), 106 (30); HRMS (EI) calcd for C₁₃H₁₇N₃: 215.1422; found: 215.1421.

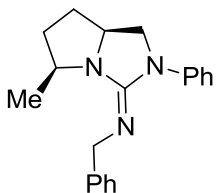
(5*S*,7*aS*)-2-Phenyl-5-(trimethylsilyl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-imine (207).



A solution of **194** (230 mg, 0.87 mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed by under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.63 mL, 8.50 mmol) and triethylamine (5.77 mL, 33.30 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 ×

10 mL). After evaporation of the combined organic extract, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield **207** as a colorless oil (78 mg, 34%); $[\alpha]_D^{20}$ –19.3 (c 0.6, CHCl₃); IR (KBr, neat) ν_{\max} 3384, 2929, 1646, 1596, 1502, 1405, 1319, 1240, 1116 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.39 (m, 2H), 7.31-7.25 (m, 2H), 7.19-7.09 (m, 1H), 3.99-3.86 (m, 2H), 3.64-3.60 (m, 1H), 2.90-2.85 (m, 1H), 2.14-2.02 (m, 2H), 1.93-1.82 (m, 1H), 1.70-1.59 (m, 2H), 0.23 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.6, 141.2, 129.3, 123.5, 121.0, 58.8, 53.3, 51.2, 31.0, 29.2, 0.1; EIMS [*m/z*(%)] 273 (M⁺, 9), 258 (100), 200 (72), 182 (47), 73 (44); HRMS (EI) calcd for C₁₅H₂₃N₃Si: 273.1661; found: 273.1669.

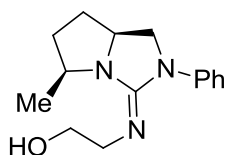
(*E*)-*N*-((5*S*,7*aS*)-5-Methyl-2-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-ylidene)-1-phenylmethanamine (203).



A solution of **166** (110 mg, 0.51mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of benzylamine (0.07 mL, 0.61 mmol) and triethylamine (0.14 mL, 1.02 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield **203** as colorless oil (95 mg, 61%) $[\alpha]_D^{20}$ –49.0 (c 0.35, CHCl₃); IR (KBr, neat) ν_{\max} 2996, 1683, 1517, 1469, 1332, 1195, 1006, 782, 640, 497 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.81-7.78 (d, 2H, *J* = 7.9 Hz), 7.56-7.53 (d, 2H, *J* = 7.4 Hz), 7.42-7.25 (m,

5H), 7.39-6.96 (t, 1H, $J = 7.4$ Hz), 4.71 (d, 1H, $J = 15.8$ Hz), 4.53 (d, 1H, $J = 15.8$ Hz), 4.20-4.04 (m, 2H), 3.92 (t, 1H, $J = 8.3$ Hz), 3.64 (t, 1H, $J = 8.9$ Hz), 2.42-2.30 (m, 1H), 2.22-2.13 (m, 1H), 1.95 (dd, 1H, $J = 5.7, 6.5$ Hz), 1.87-1.79 (m, 1H), 1.18 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75.5 MHz, CDCl_3); δ 152.7, 143.1, 142.3, 128.4, 128.1, 127.4, 125.9, 121.1, 118.6, 58.4, 55.8, 55.0, 52.9, 35.5, 28.6, 19.3. ; EIMS [$m/z(\%)$] 305 (M^+ , 38), 250 (53), 215 (37), 160 (100), 105 (66), 91 (84), 77 (70). HRMS (EI) calcd for $\text{C}_{20}\text{H}_{23}\text{N}_3$: 305.1892; found: 305.1895.

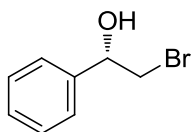
2-((*E*)-((5*S*,7*aS*)-5-Methyl-2-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazol-3(2*H*)-ylidene)amino)ethanol (204).



A solution of **166** (190 mg, 0.88 mmol) in POCl_3 (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl_3 was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of ethanolamine (0.07 mL, 0.61 mmol) and triethylamine (0.14 mL, 1.02 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH_2Cl_2 (3×10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3×10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH_2Cl_2 (4×15 mL). The combined organic extract dried over anhyd. Na_2SO_4 , filtered, and concentrated under reduced pressure to yield **204** as colorless oil (71 mg, 31 %) $[\alpha]_{\text{D}}^{20} +10.1$ (c 0.35, CHCl_3); IR (KBr, neat) ν_{max} 3394, 2939, 1639, 1596, 1502, 1400, 1259, 1189, 1145, 1016, 892, 752, 514 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.61 (d, 2H, $J = 7.8$ Hz), 7.31 (dd, 2H, $J = 8.9$ Hz), 6.96 (t, 1H, $J = 7.3$ Hz), 4.14-4.06 (m, 1H), 3.96-3.87 (m, 2H), 3.81-3.75 (dd, 2H, $J = 7.0, 4.6$ Hz), 3.61 (t, 1H, $J = 9.0$ Hz), 3.52-3.34 (m, 2H), 2.84 (b, 1H), 2.37-2.24 (m, 1H), 2.19-2.11 (m, 1H), 1.92 (dd, 1H, $J = 6.6, 5.2$ Hz), 1.86-1.74 (m, 1H), 1.09 (d, 3H, $J = 6.4$ Hz); ^{13}C NMR (75.5 MHz, CDCl_3); δ 153.6, 142.0, 128.5, 121.6, 118.9, 63.4,

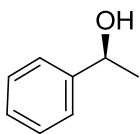
58.3, 55.8, 54.5, 50.5, 35.4, 28.5, 19.2 ; EIMS [m/z(%)] 259 (M⁺, 10.4), 228 (100), 153 (12). HRMS (EI) calcd for C₁₅H₂₁N₃O: 259.1682; found: 259.1684.

(+)-(S)-2-Bromo-1-phenylethanol (99).



A solution of guanidine **205** (27 mg, 0.10 mmol) in toluene (3 mL) at room temperature was treated with added BH₃•SMe₂ (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction mixture was heated at 110 °C for 20 min. A solution of phenacyl bromide (100 mg, 0.50 mmol) in toluene (2 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave **(R)-99** as a colorless oil (84 mg, 83%); [α]_D²⁰ +3.6 (c 1.00, CHCl₃) [lit.⁸³ [α]_D²⁵ -39.0 (c 8.00, CHCl₃) for (*R*) enantiomer]; CSP HPLC analysis (Chiralcel OD-H, 90:10 hexanes:*i*-PrOH, 1.0 mL/min) determined an er of 54:46 (8% ee) [t_R(major) = 7.77 min, t_R(minor) = 9.03 min]; ¹H NMR (300 MHz, CDCl₃) δ 7.49–7.34 (m, 5H), 5.01–4.85 (m, 1H), 3.69–3.48 (m, 2H), 2.64 (b, 1H).

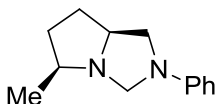
(-)-(S)-1-Phenylethanol (220b).



A solution of guanidine **207** (27 mg, 0.10 mmol) in toluene (1 mL) at room temperature was treated with added BH₃•SMe₂ (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction mixture was heated at 110 °C for 20 min. A solution of acetophenone (0.06 mL, 0.50 mmol) in toluene (1 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave **(S)-220b** as a colorless oil (47 mg, 77%); [α]_D²⁰ -10.1 (c 2.00, CHCl₃) [lit.⁸⁴ [α]_D²⁵ -57.0 (c 5.13, CHCl₃) for (*S*) enantiomer]; CSP HPLC analysis (Chiralcel OD-H, 95:5 hexanes:*i*-

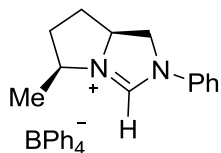
PrOH, 0.4 mL/min) determined an er of 62:38 (24% ee) [$t_R(\text{minor}) = 19.49$ min, $t_R(\text{major}) = 23.72$ min]; ^1H NMR (300 MHz, CDCl_3) δ 7.38–7.28 (m, 5H), 4.95–4.90 (m, 1H), 1.80–1.79 (b, 1H), 1.44 (d, 3H, $J = 6.5$ Hz).

(5*S*,7*aS*)-5-Methyl-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazole (167).



A solution of **166** (600 mg, 2.77 mmol) in THF (150 mL) at -78 °C was treated with DIBAL-H (24 mL, 1.00 M, 22.22 mmol) and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of saturated solution of potassium sodium tartrate (10 mL) and water (135 mL), and extracted with CH_2Cl_2 (4×100 mL). The combined organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 97:3 EtOAc: Et_3N , $R_f = 0.27$) gave **167** as a colorless oil (289 mg, 52%); $[\alpha]_D^{20} +14.2$ (c 1, CHCl_3); IR (KBr, neat) ν_{max} 3053, 3039, 2953, 2904, 2870, 2836, 1596, 1504, 1365, 1341, 1154, 1120, 992, 742, 688, 511 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (t, 2H, $J = 8.1$ Hz), 6.74 (t, 1H, $J = 7.5$ Hz), 6.57–6.54 (d, 2H, $J = 8.0$ Hz), 4.37–4.30 (d, 1H, $J = 6.8$ Hz), 4.13 (d, 1H, $J = 6.8$ Hz), 3.91–3.85 (m, 1H), 3.52–3.40 (m, 2H), 3.11–3.07 (m, 1H), 2.20–2.07 (m, 1H), 2.04–1.93 (m, 1H), 1.87–1.70 (m, 1H), 1.68–1.62 (m, 1H), 1.3 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (75.5 MHz, CDCl_3) δ 146.7, 129.2, 116.6, 112.4, 64.4, 63.8, 58.0, 53.7, 32.2, 30.0, 16.9; EIMS [$m/z(\%)$] 217 (M^+ , 14), 201 (74), 69 (100), 55 (48). HRMS (EI) calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2$: 216.1262; found: 216.1262.

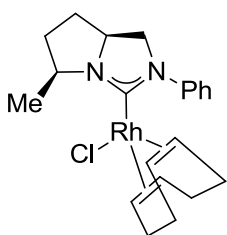
(5*S*,7*aS*)-5-Methyl-2-phenyl-1,2,5,6,7,7*a*-hexahydropyrrolo[1,2-*c*]imidazol-4-ium tetraphenylborate (168).



A solution of **167** (202 mg, 1.00 mmol) and tritylium tetrafluoroborate (330 mg, 1.00 mmol) in CH_2Cl_2 (12 mL) was stirred at room temperature for 16 h in a sealed tube under argon. The mixture was cooled to room temperature and CH_2Cl_2 was removed under reduced pressure. The crude mixture was dissolved in MeOH (3 mL), and a solution of NaBPh_4 (342 mg, 1.00 mmol) in MeOH (3 mL) was added dropwise. The resulting precipitate

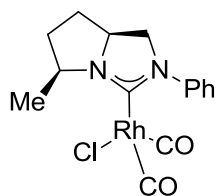
was filtered, washed with cold MeOH and dried under high vacuum to give **168** as a beige powder (33 mg, 63%); mp 189-192 °C; $[\alpha]_D^{20} +149.0$ (c 0.5, CHCl₃); IR (KBr) ν_{\max} 3051, 1608, 1587, 1502, 1477, 1425, 1315, 1280, 1251, 1135, 1066, 1031, 1007, 946, 847, 823, 734, 705, 604, 512 cm⁻¹; ¹H NMR (300 MHz, acetone-d₆): 9.15 (s, 1H), 7.68 (d, 1H, *J* = 8.3 Hz), 7.36 (d, 11H, *J* = 5.8 Hz), 6.94 (t, 9H, *J* = 7.0 Hz), 6.80 (t, 4H, *J* = 7.2 Hz), 4.79-4.70 (m, 1H), 4.50-4.35 (m, 2H), 4.15 (d, 1H, *J* = 6.5 Hz), 2.50-2.25 (m, 2H), 2.01-1.81 (m, 2H), 1.60 (d, 3H, *J* = 6.2 Hz); ¹³C NMR (75.5 MHz, acetone-d₆): 164.3 (q, ¹J¹³C-¹¹B = 49.2 Hz), 152.2, 136.1, 132.7, 129.8, 125.2, 125.1, 121.4, 119.9, 64.6, 64.5, 54.9, 54.2, 33.4, 18.2; FABMS [*m/z*(%)] 201 (M-BPh₄, 100), 149 (9), 41 (84); HRMS (ESI) calcd for C₁₃H₁₇N₂: 201.1398; found: 201.1392.

Chloro(η^4 -1,5-cyclooctadiene)(5-methyl-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-2-ylidene)rhodium (240**).**



A solution of **168** (50 mg, 0.10 mmol) and [Rh(COD)Cl]₂ (25 mg, 0.05 mmol) in THF (2 mL) was stirred at -78 °C in a sealed tube under argon. After 30 min sodium hydride (5 mg, 60% dispersion in mineral oil, 0.12 mmol) was added. The mixture was stirred at room temperature for 16 h, during which time the color changed from orange to brown. After removing the solvent on a rotary evaporator, the crude product was purified by column chromatography (silica gel, 7:3 hexane:EtOAc, *R_f* = 0.21) gave **240** as a 56:44 mixture of coordination isomers as an orange-yellow oil in a 3:1 ratio. (25 mg, 58%); $[\alpha]_D^{20} -21.0$ (c 1.5, CHCl₃); IR (KBr, neat) ν_{\max} 3341, 3047, 2920, 2870, 2828, 2116, 1943, 1598, 1555, 1494, 1469, 1364, 1230, 1183, 1084, 1021, 995, 958, 863, 814, 756, 694, 644, 516 cm⁻¹; Main isomer: ¹H NMR (300 MHz, CDCl₃) δ 8.07 (d, 1H, *J* = 7.7 Hz), 7.47-7.39 (m, 2H), 7.25-7.17 (m, 2H), 5.15-5.08 (m, 1H), 5.03-4.96 (m, 1H), 4.36-4.20 (m, 1H), 4.16-3.96 (m, 1H), 3.79-3.72 (m, 2H), 3.24-3.18 (m, 1H), 2.51-2.14 (m, 3H), 2.23 (d, 3H, *J* = 6.5 Hz), 2.07-1.54 (m, 10H); ¹³C NMR (75.5 MHz, CDCl₃) δ 204.6, 143.5, 128.3, 124.8, 120.8, 97.7, 97.4, 72.0, 69.7, 66.9, 65.4, 55.1, 51.7, 36.3, 32.1, 29.1, 28.6, 27.5, 22.4; EIMS [*m/z*(%)] 446 (M⁺, 2.2), 411 (12.2), 302 (18.4), 201 (33.7), 55 (100). HRMS (EI) calcd for C₂₁H₂₈N₂RhCl: 446.1021; found: 446.1029.

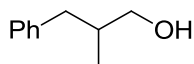
Dicarbonylchloro)(5-methyl-2-phenylhexahydro-1*H*-pyrrolo[1,2-*c*]imidazolidine-2-ylidene)rhodium (242).



To a solution of **240** (60 mg, 0.13 mmol) in DCM (7 mL) carbon monoxide was bubbled into the reaction mixture. The mixture was stirred at room temperature for 16 h under CO atmosphere, during which time the color changed from orange to red.

After removing the solvent on a rotary evaporator, the crude product was purified by column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.26$) gave **242** as an orange-yellow oil mixture of rotamers in a roughly 10:1 ratio. (40 mg, 78%); $[\alpha]_D^{20} -33.1$ (c 1.8, CHCl_3); IR (KBr, neat) ν_{max} 3150, 2922, 2873, 2068, 1987, 1596, 1479, 1454, 1401, 1369, 1343, 1309, 1237, 1187, 754, 691, 634, 579, 510 cm^{-1} ; Main isomer: ^1H NMR (300 MHz, CDCl_3) δ 7.69 (d, 1H, $J = 7.49$ Hz), 7.37 (t, 2H, $J = 8.2$ Hz), 7.28-7.22 (m, 2H), 4.54-4.40 (m, 1H), 4.29-4.22 (m, 1H), 4.06 (dd, 1H, $J = 9.8, 3.2$ Hz), 3.96-3.81 (m, 1H), 2.53-2.39 (m, 1H), 2.20-2.14 (m, 1H), 2.05-1.99 (m, 1H), 1.83 (d, 3H, $J = 7.0$ Hz), 1.80-1.74 (m, 1H); ^{13}C NMR (75.5 MHz, CDCl_3) δ 197.1 (d, $J = 40.1$ Hz), 186.2 (d, $J = 55.0$ Hz), 182.8 (d, $J = 75.1$ Hz), 142.2, 128.6, 125.7, 121.4, 66.8, 55.7, 51.8, 36.2, 28.0, 23.9; HRMS (EI) $[\text{M}-\text{Cl}-2\text{CO}]$ calcd for $\text{C}_{15}\text{H}_{16}\text{ClN}_2\text{O}_2\text{Rh}$: 303.0356; found: 303.0369.

2-Methyl-3-phenylpropan-1-ol (245).



A solution of **242** (4 mg, 0.01 mmol, 0.2 mol%), allyl benzene **243** (0.07 mL, 0.5 mmol) and (triphenyl phosphite (0.02 mL, 0.01 mmol, 2 mol%) in toluene (2 mL) was placed into the bomb under 20 bar of CO/H_2 pressure at 60 °C and stirred for 48 h. The crude reaction was dissolved in EtOH (4 mL) and NaBH_4 (111 mg, 3.00 mmol) was added. The reaction mixture was stirred at room temperature for 4 h and worked up by careful addition of 5% aqueous HCl (4 mL). The crude mixture was extracted with CH_2Cl_2 (3×10 mL), and the combined organic phase was dried over anhyd. Na_2SO_4 , filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 4:1 hexane:EtOAc, $R_f = 0.41$) gave combined yield of both branched and linear alcohols as a

colourless oil (212 mg, 54%); ^1H NMR (300 MHz, CDCl_3): δ 3.59-3.47 (m, 2H), 2.79 (dd, 1H, $J = 13.4$, 6.3 Hz), 2.44 (dd, 1H, $J = 13.4$, 8.1 Hz), 2.03-1.94 (m, 1H), 1.45 (br, 1H), 0.94 (d, 3H, $J = 6.8$ Hz).

4-phenylbutan-1-ol (244). ^1H NMR (300 MHz, CDCl_3): δ 7.33-7.20 (m, 5H), 3.68 (t, 2H, $J = 6.5$ Hz), 2.67 (t, 2H, $J = 7.6$ Hz), 1.76- 1.61 (m, 4H), 1.45 (br s, 1H).

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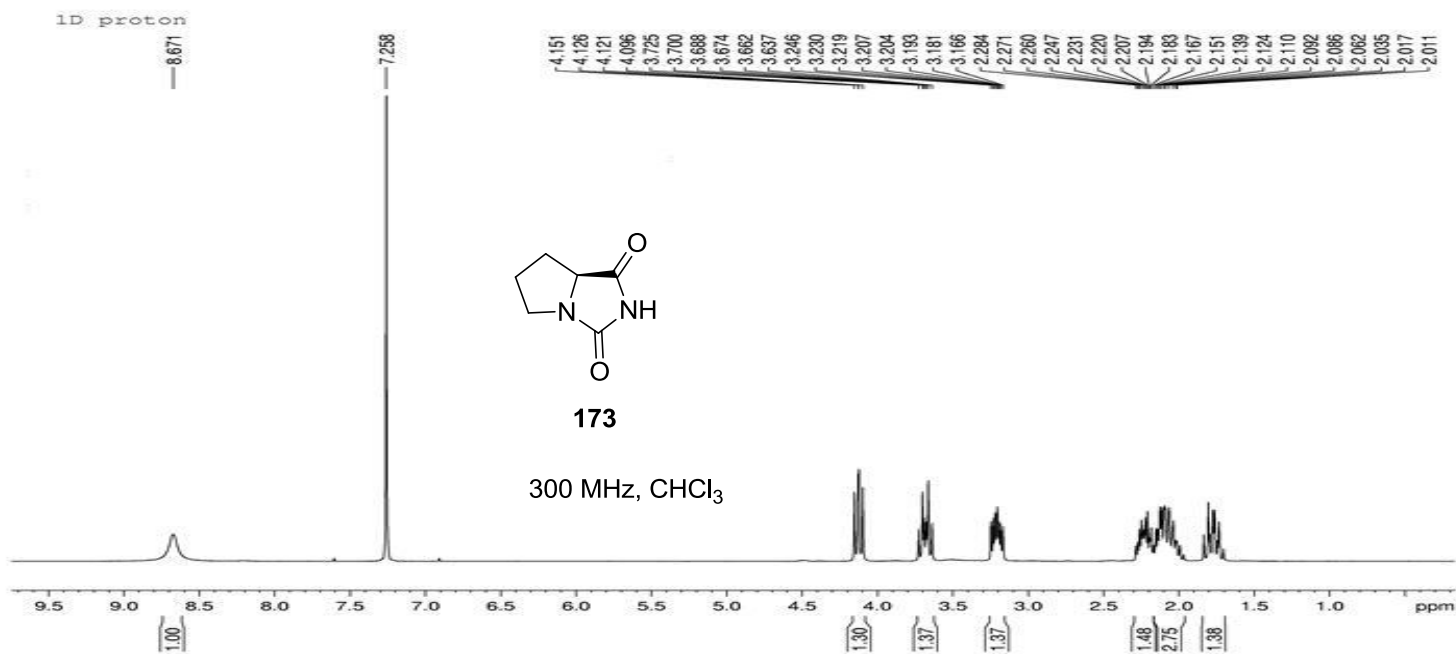
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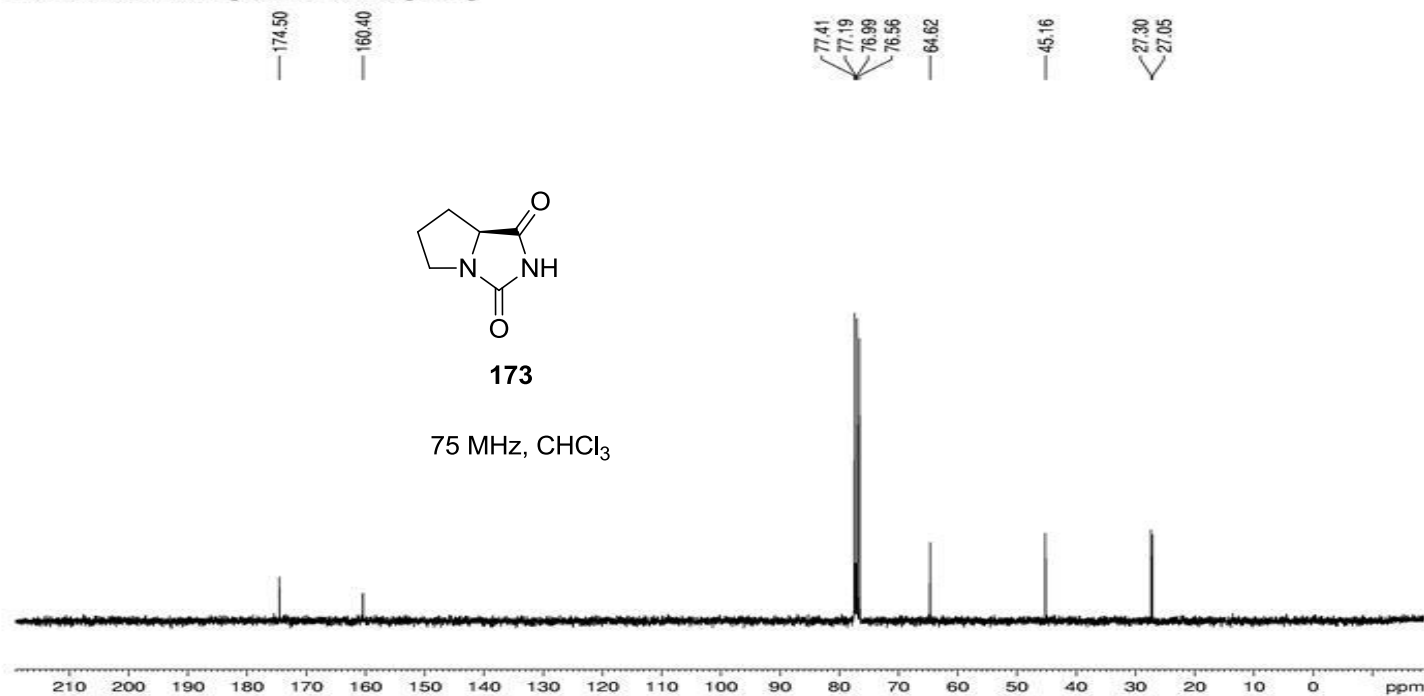
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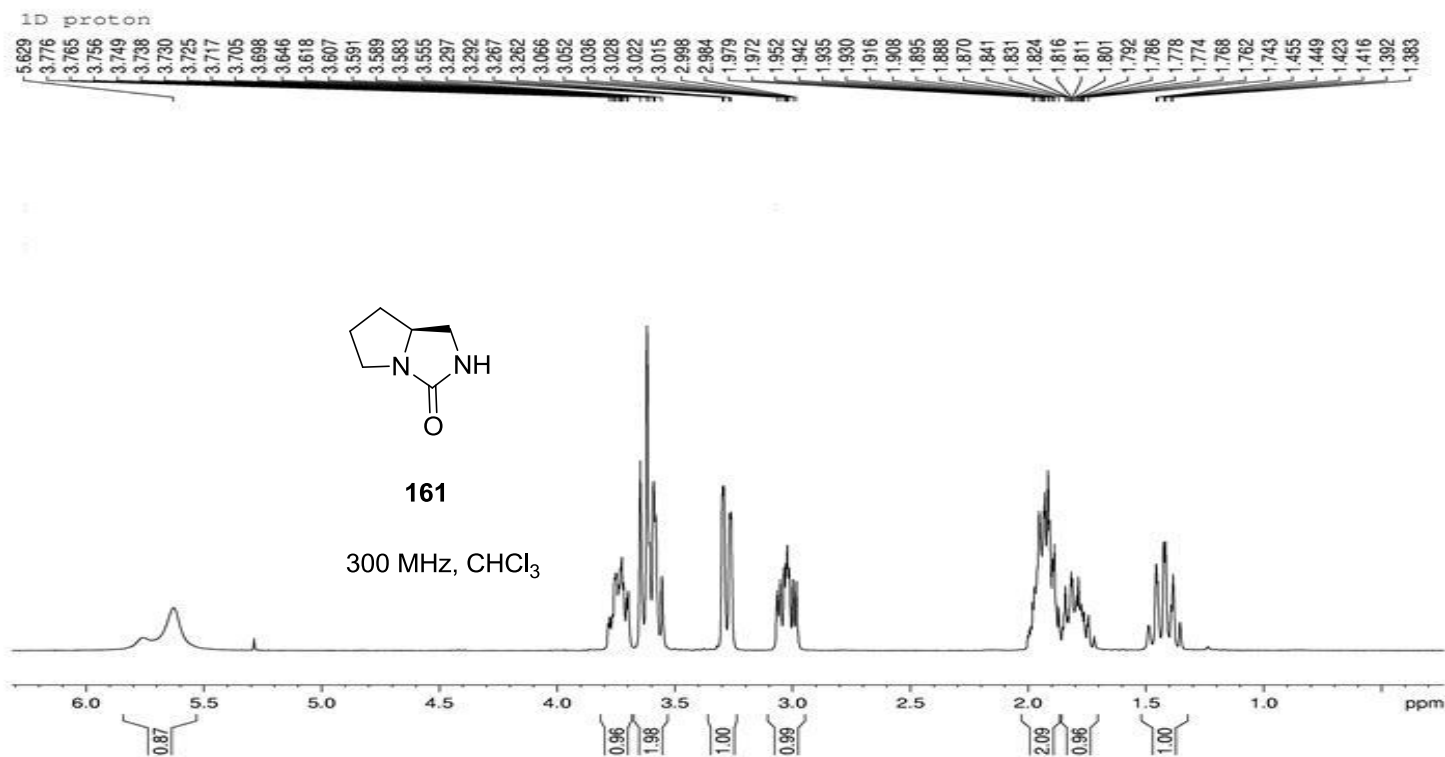
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6. Appendix: Spectra

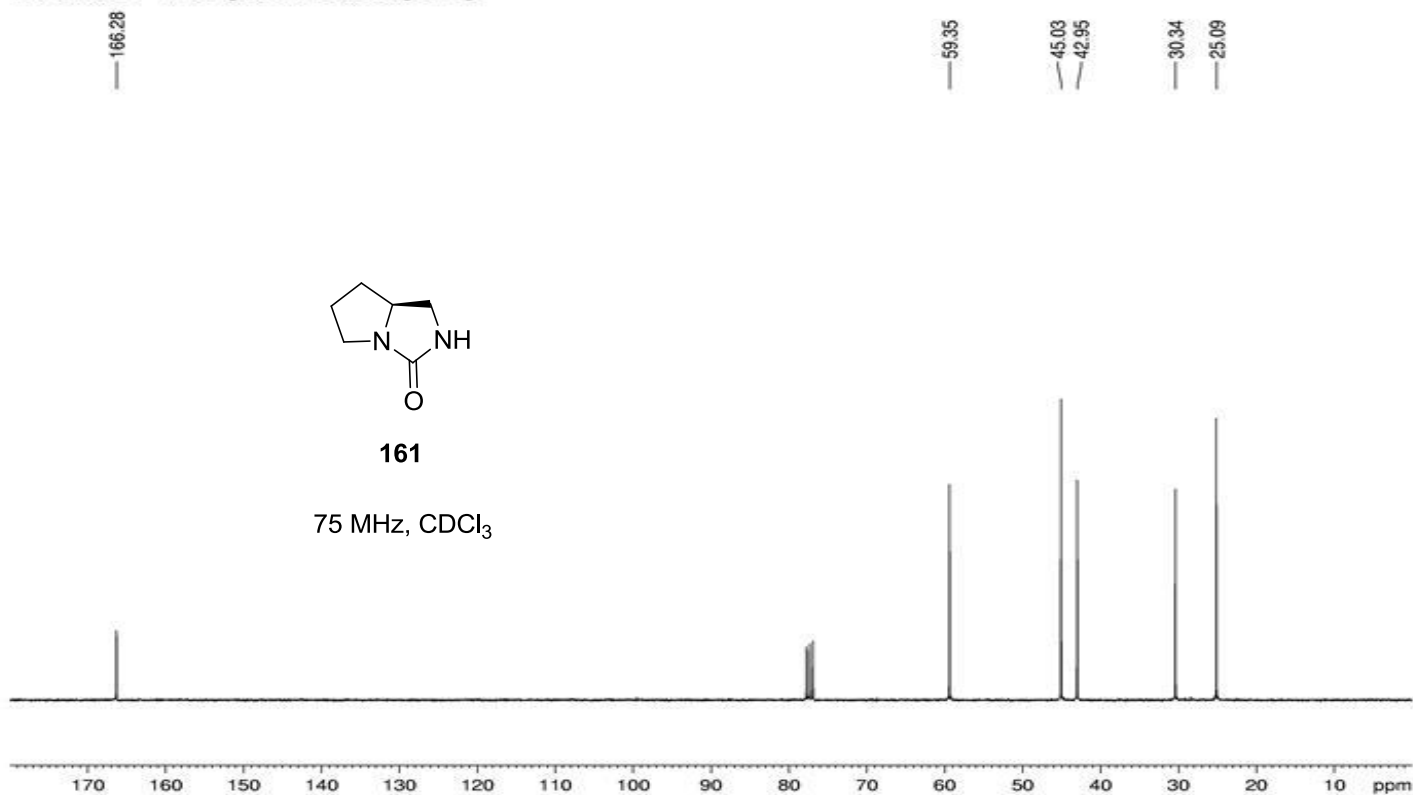


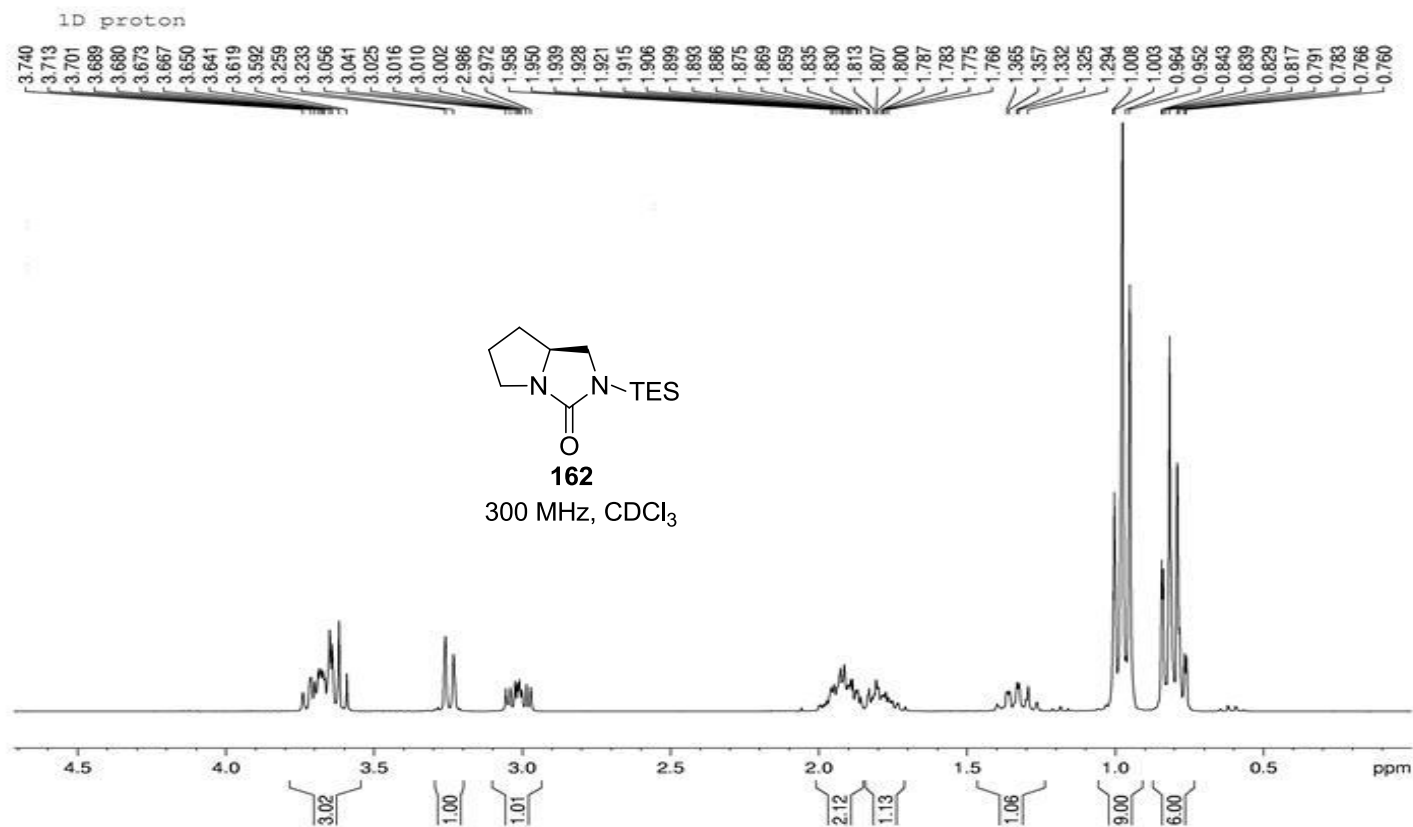
1D carbon with proton decoupling



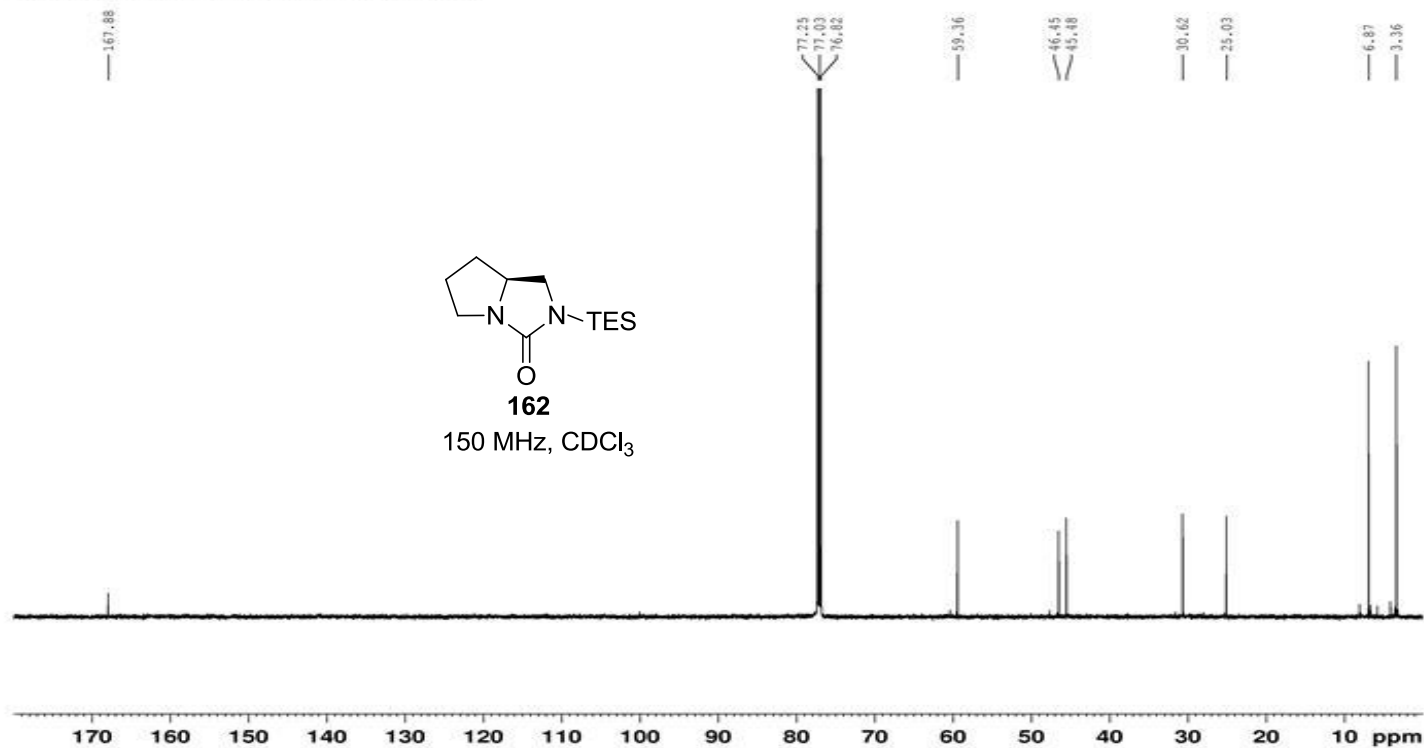


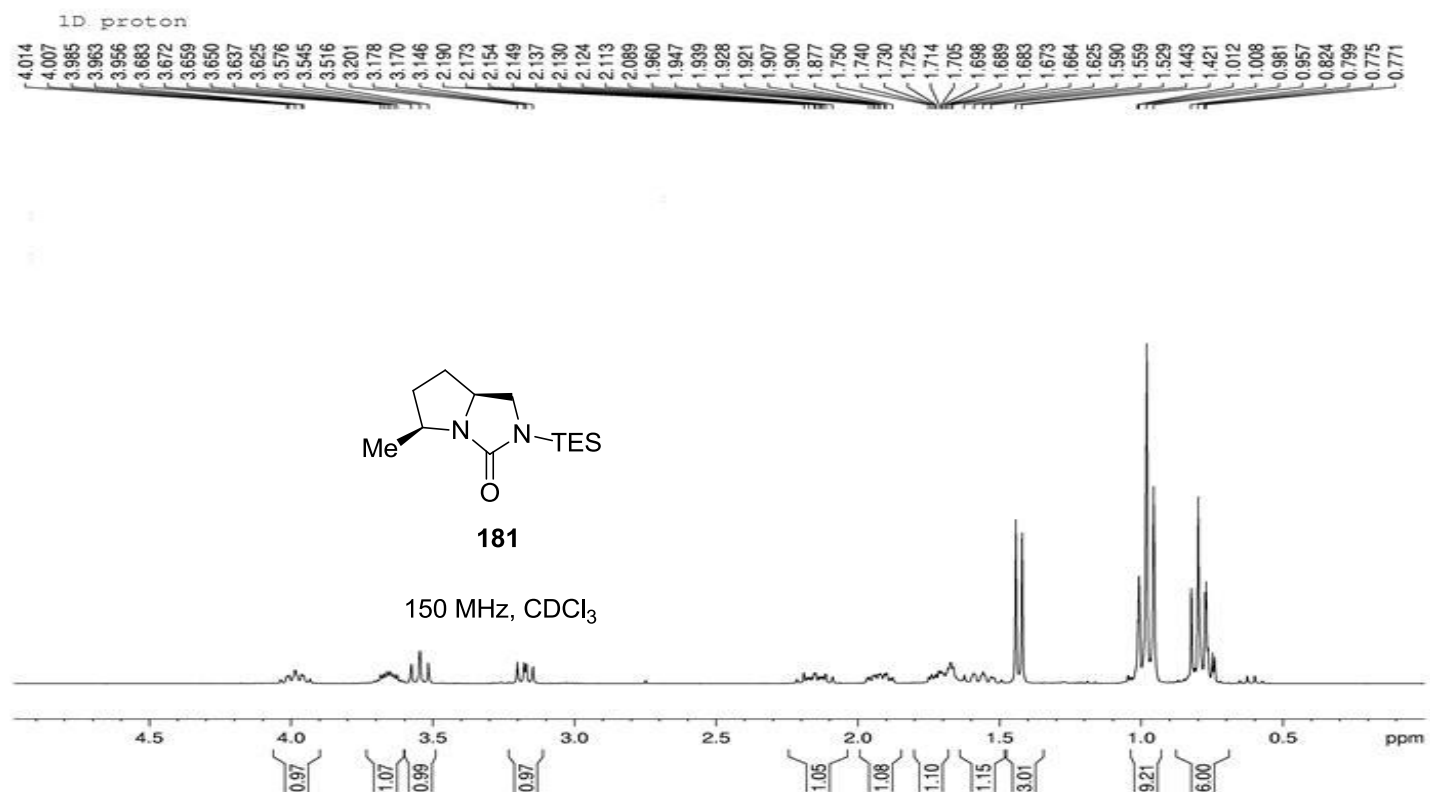
1D carbon with proton decoupling



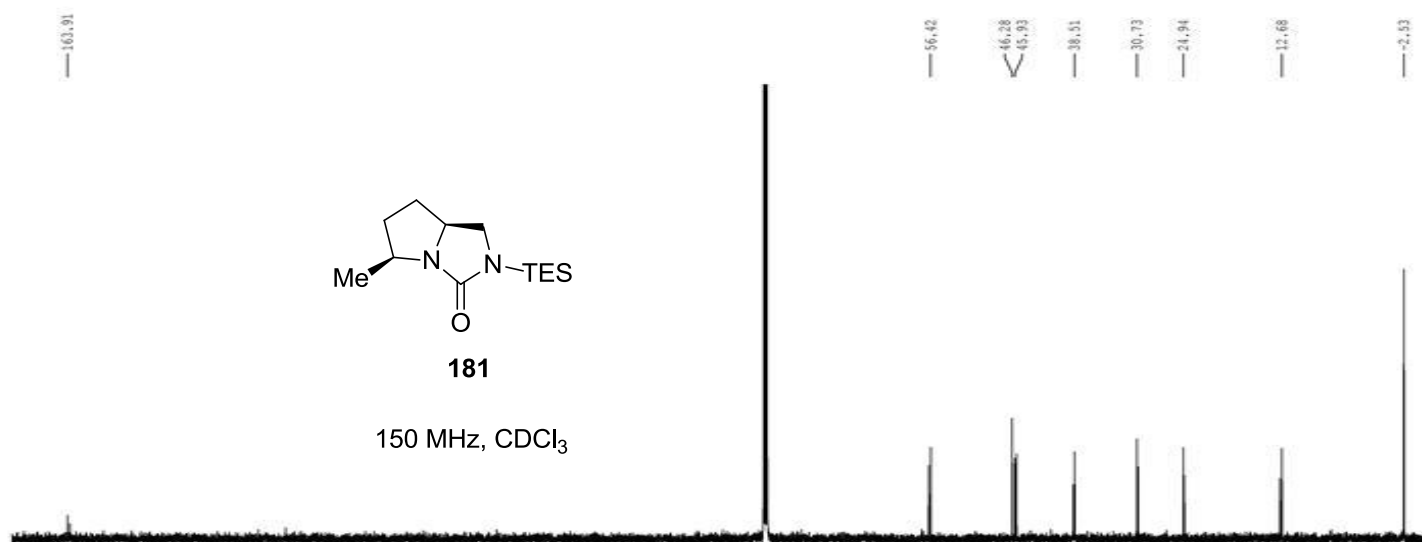


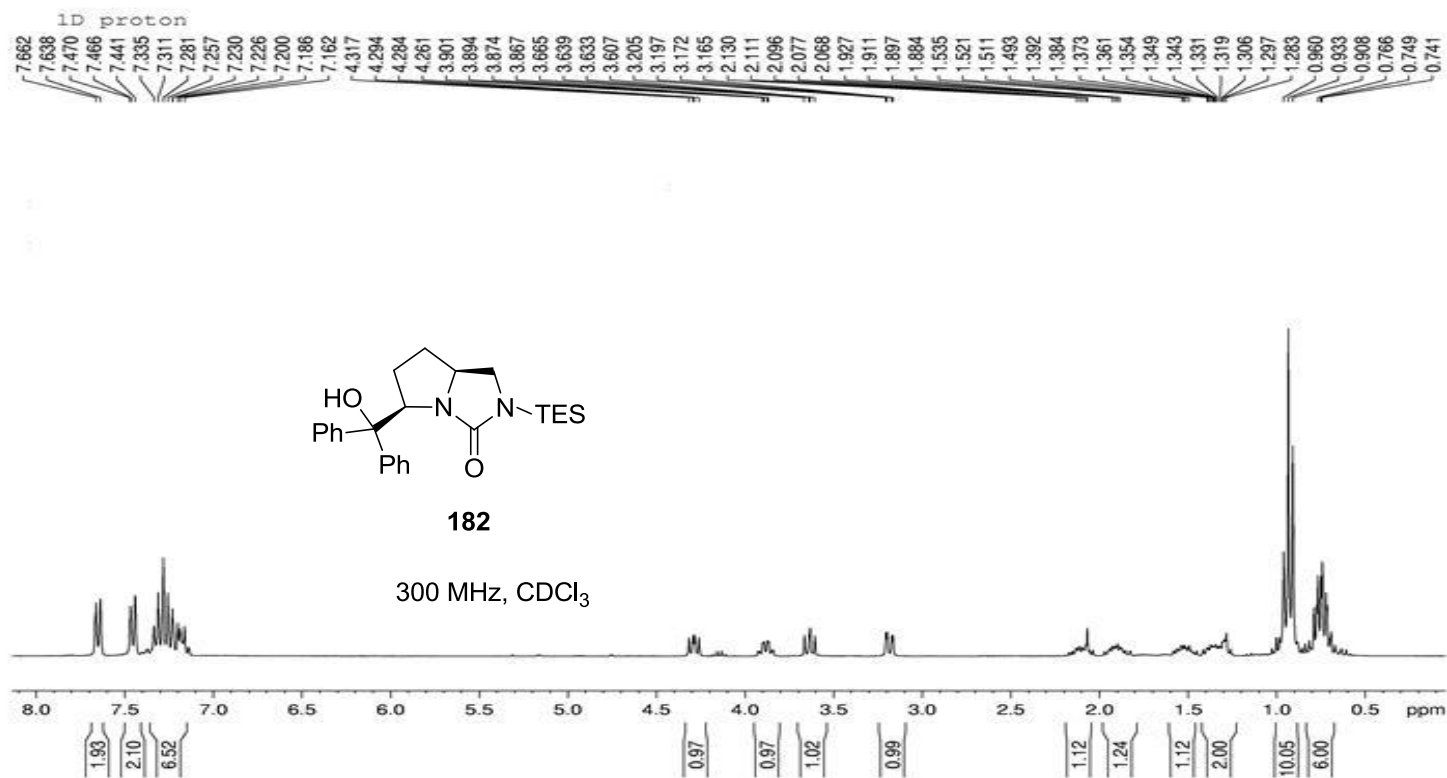
1d carbon with proton decoupling



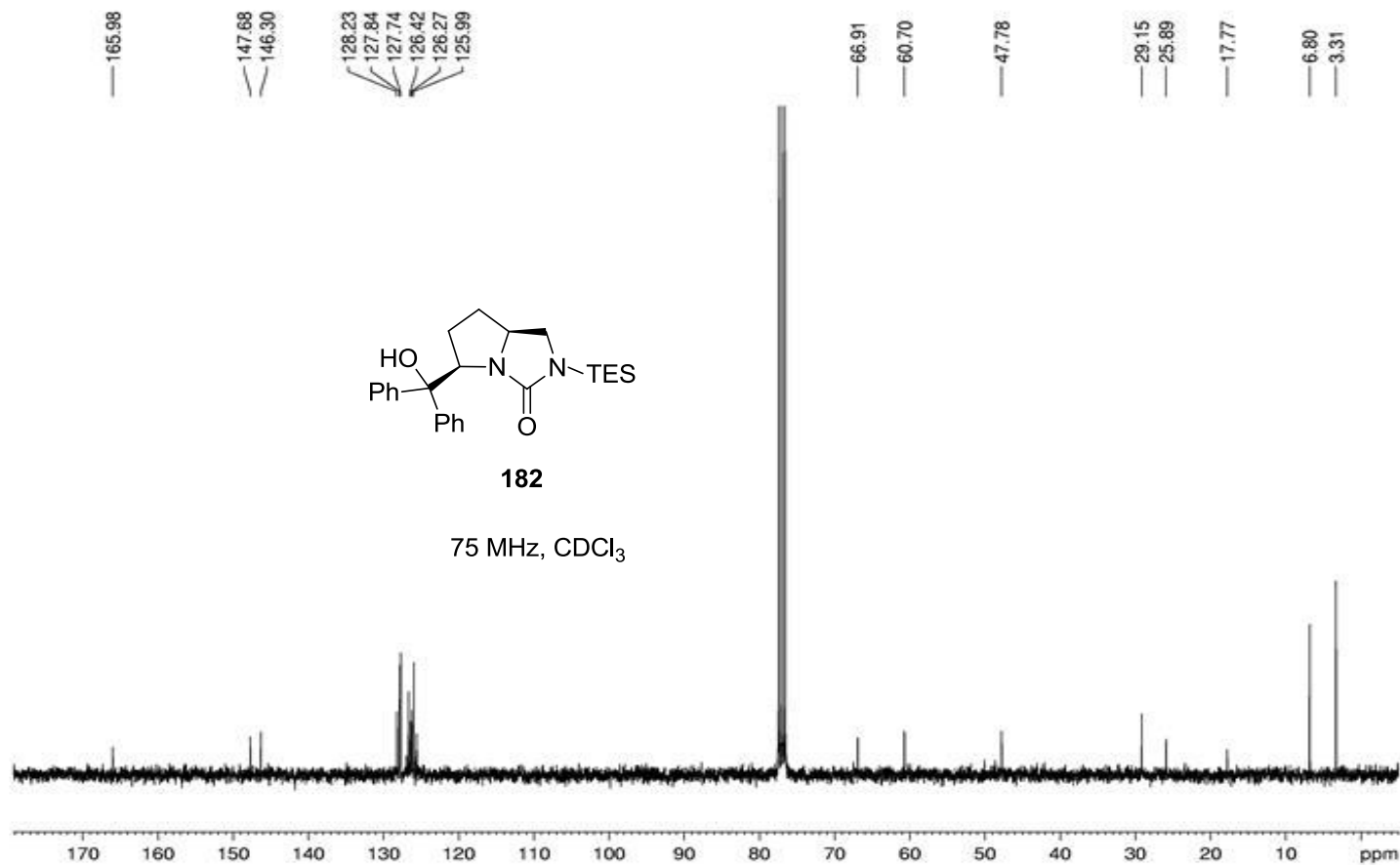


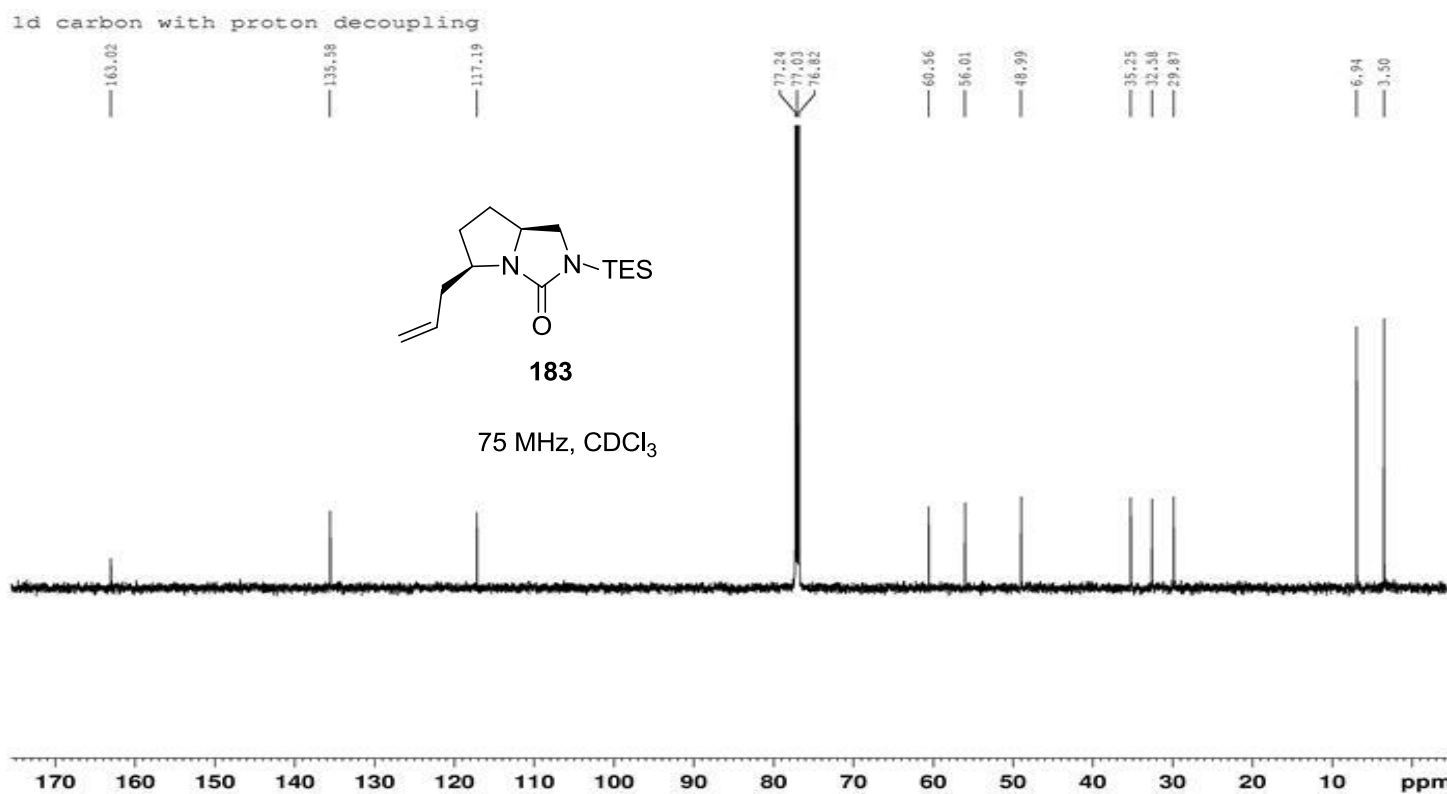
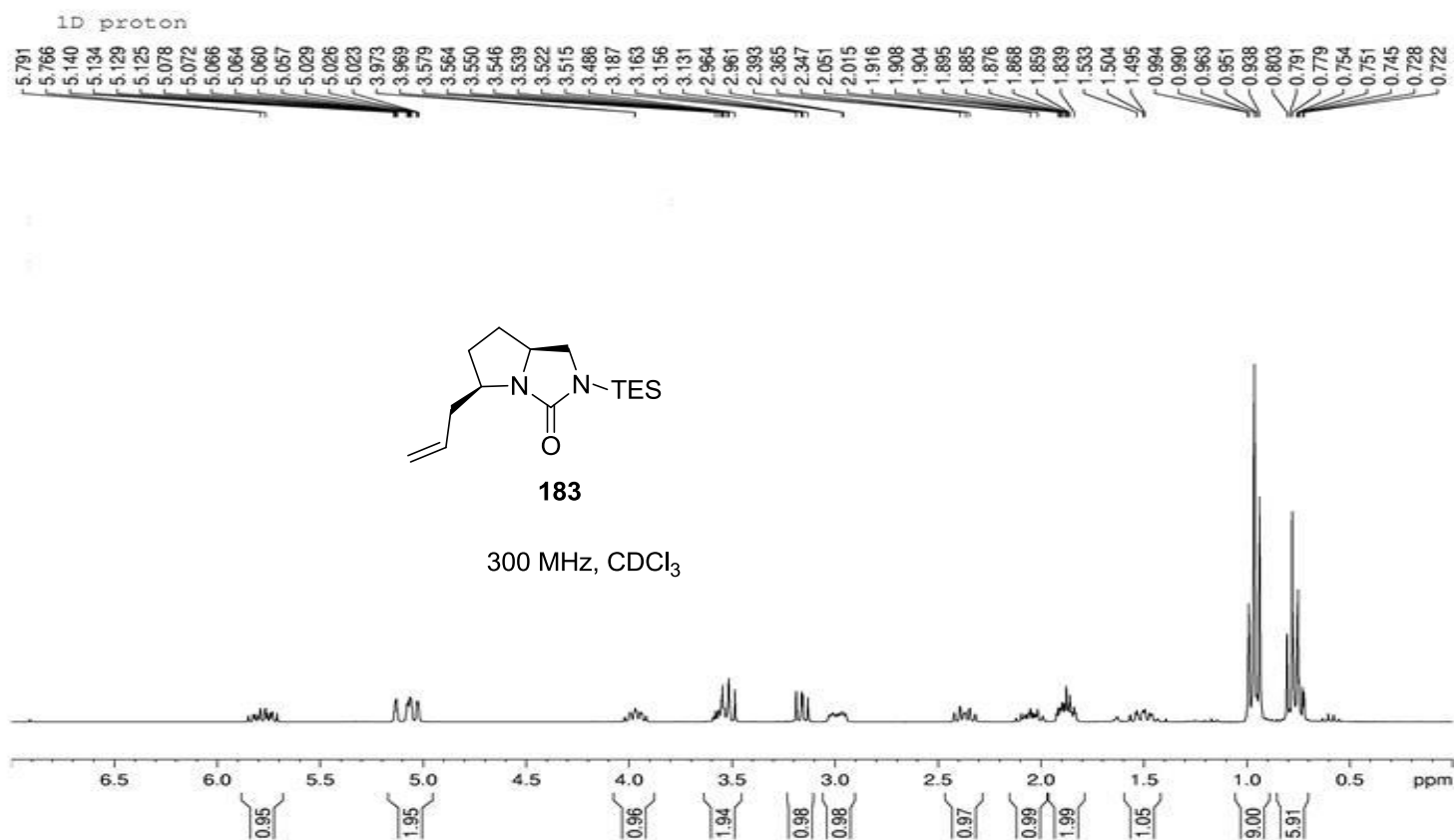
1d carbon with proton decoupling



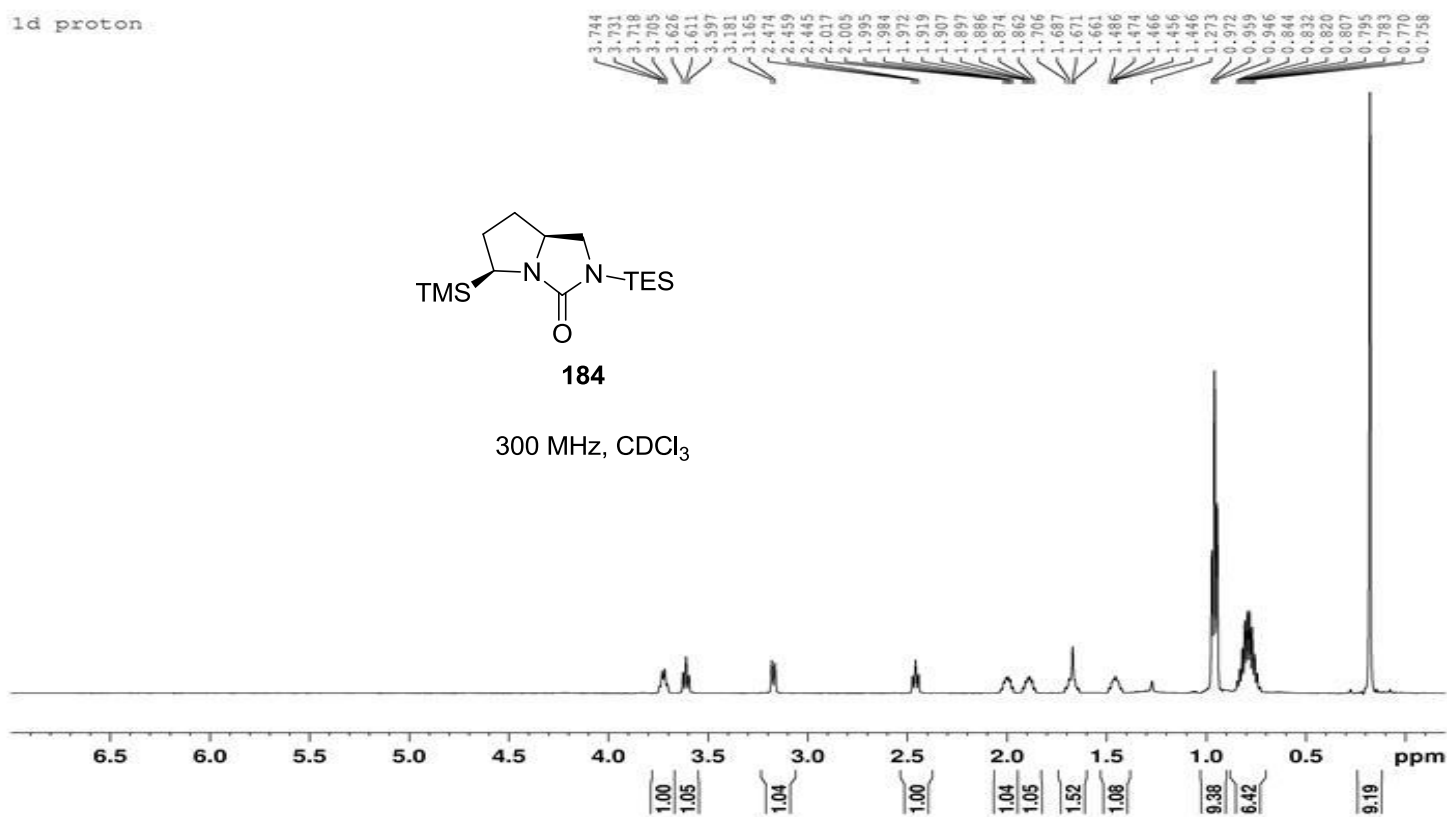


1D carbon with proton decoupling

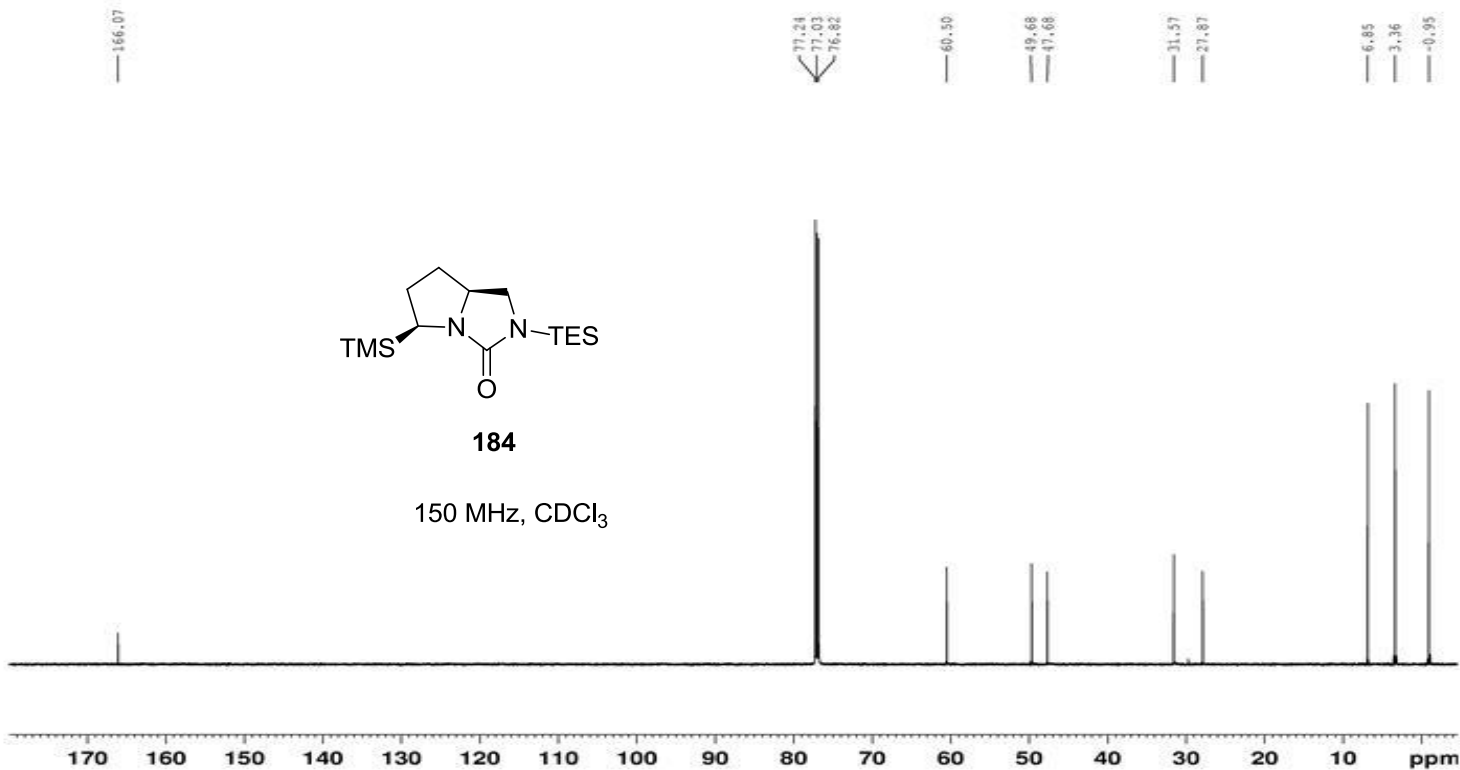


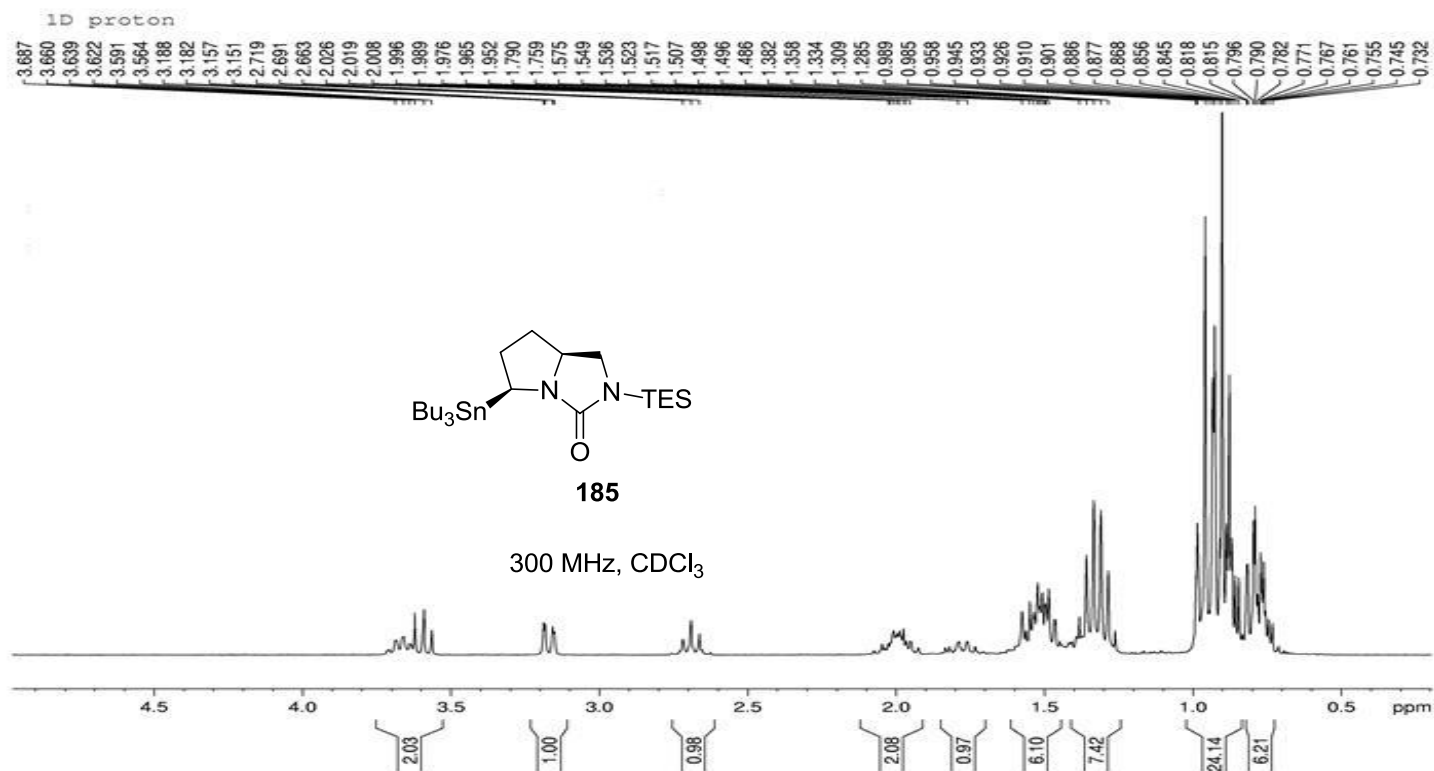


1d proton

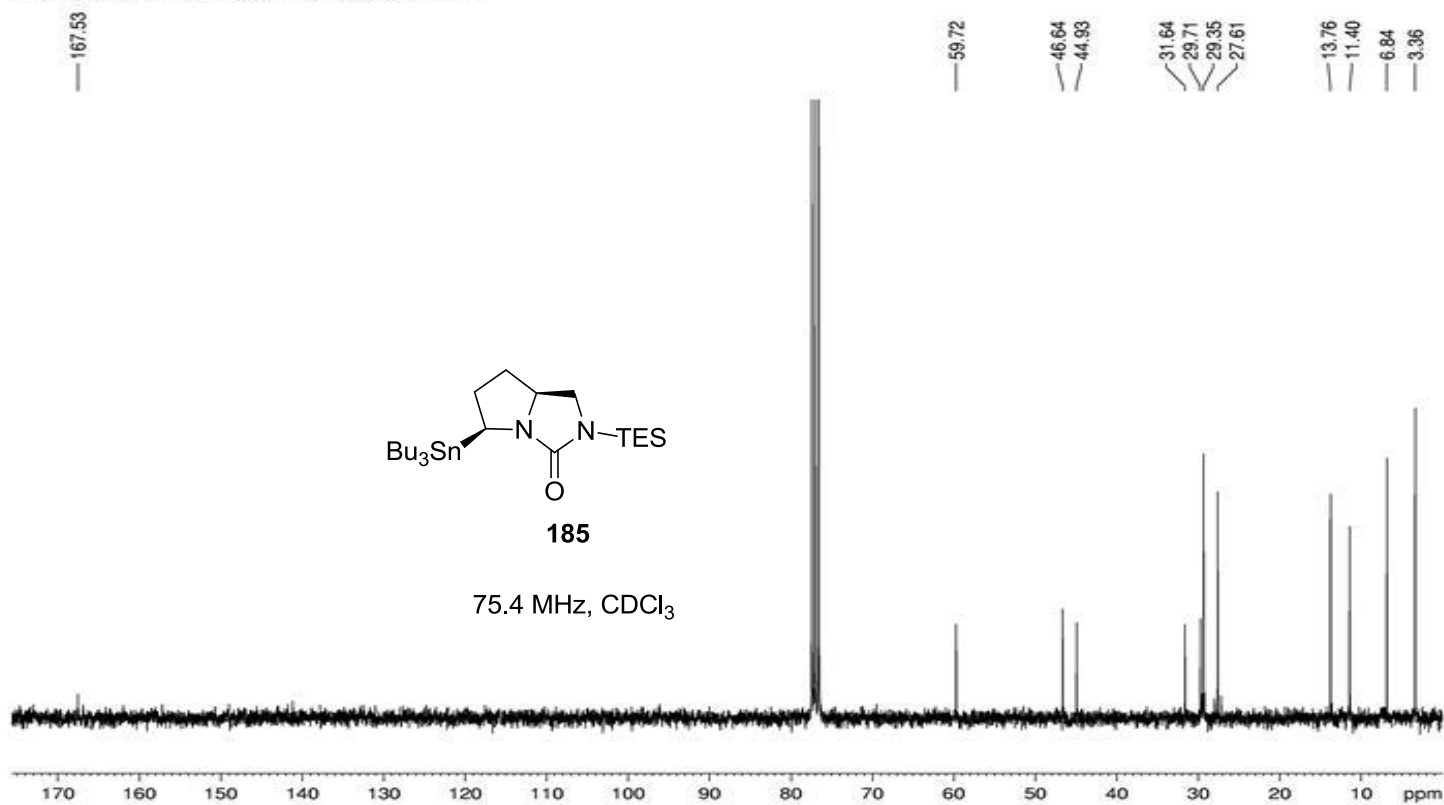


1d carbon with proton decoupling

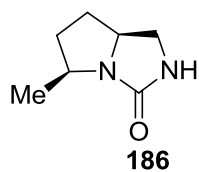




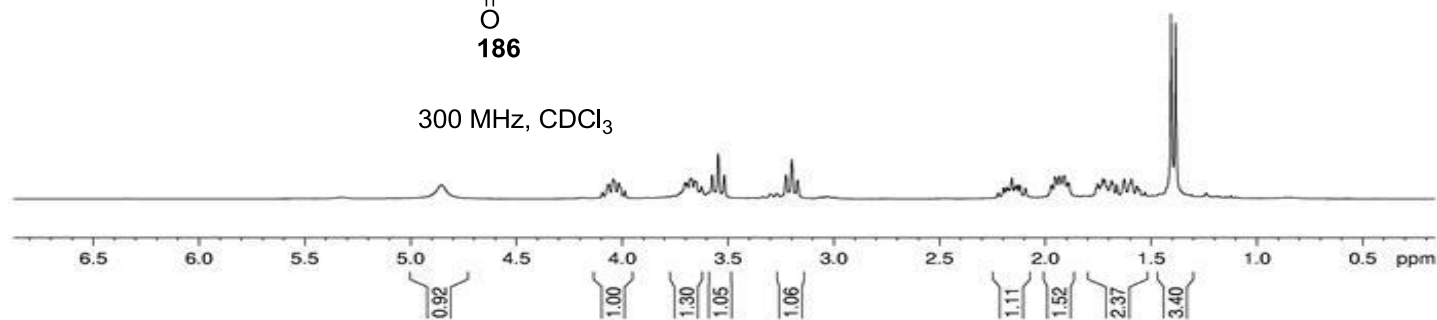
1D carbon with proton decoupling



1D proton



300 MHz, CDCl₃



1d carbon with proton decoupling

162.04

77.26
77.05
76.84

60.89

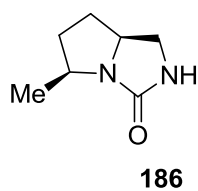
51.83

45.97

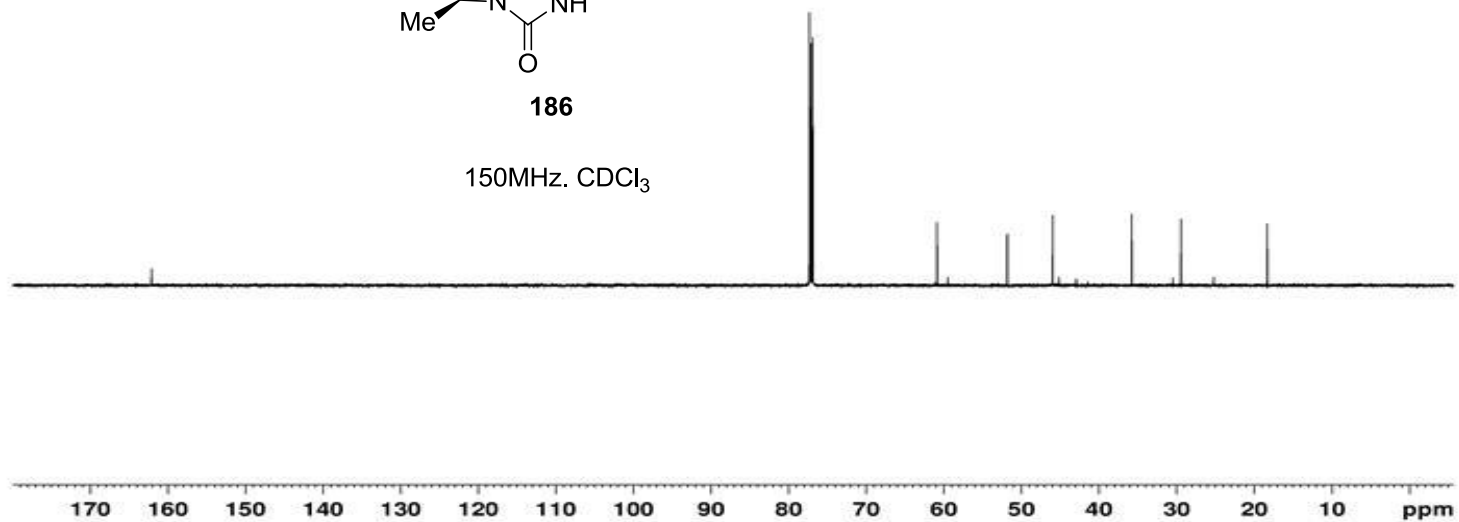
35.79

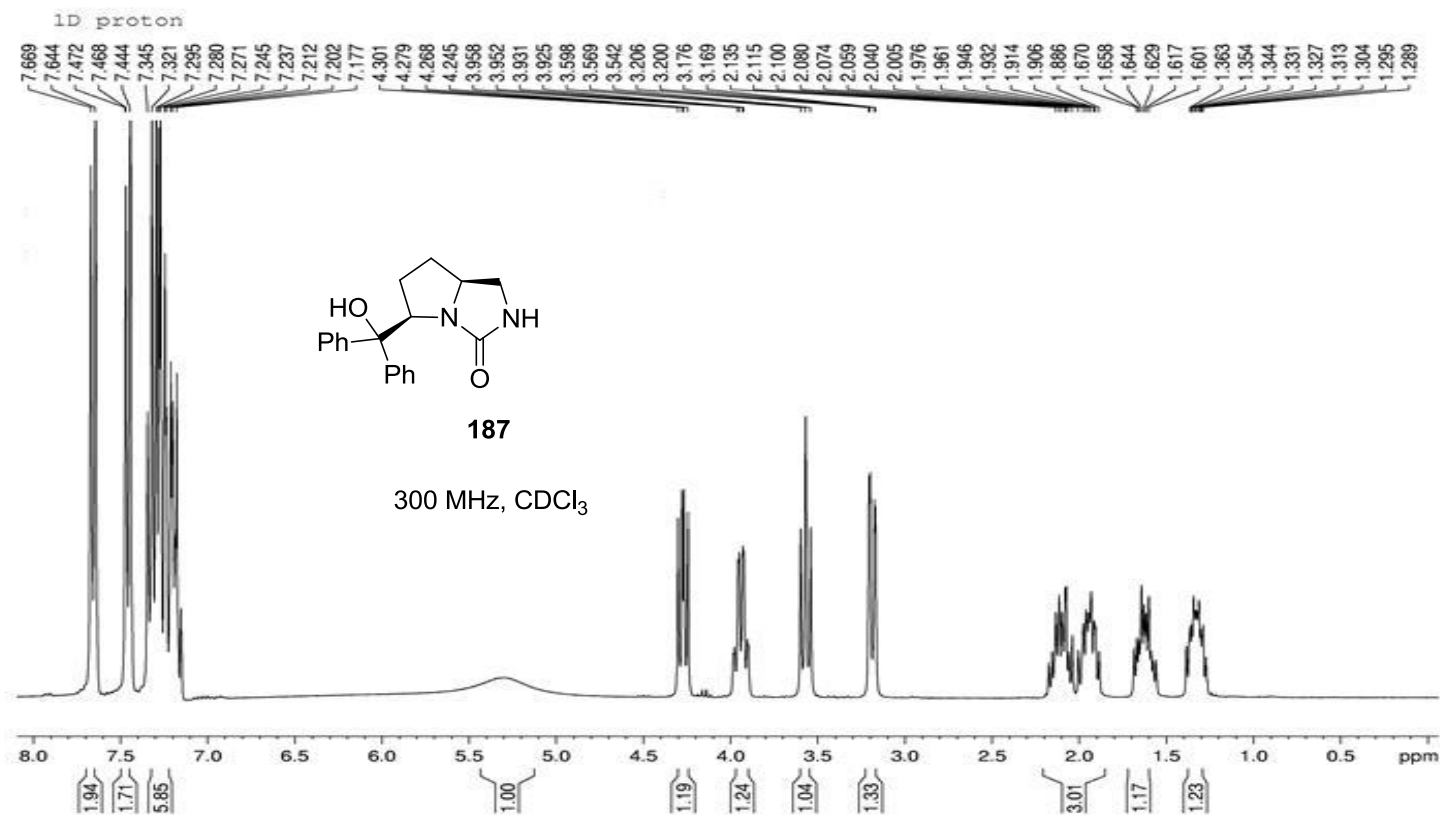
29.46

18.33

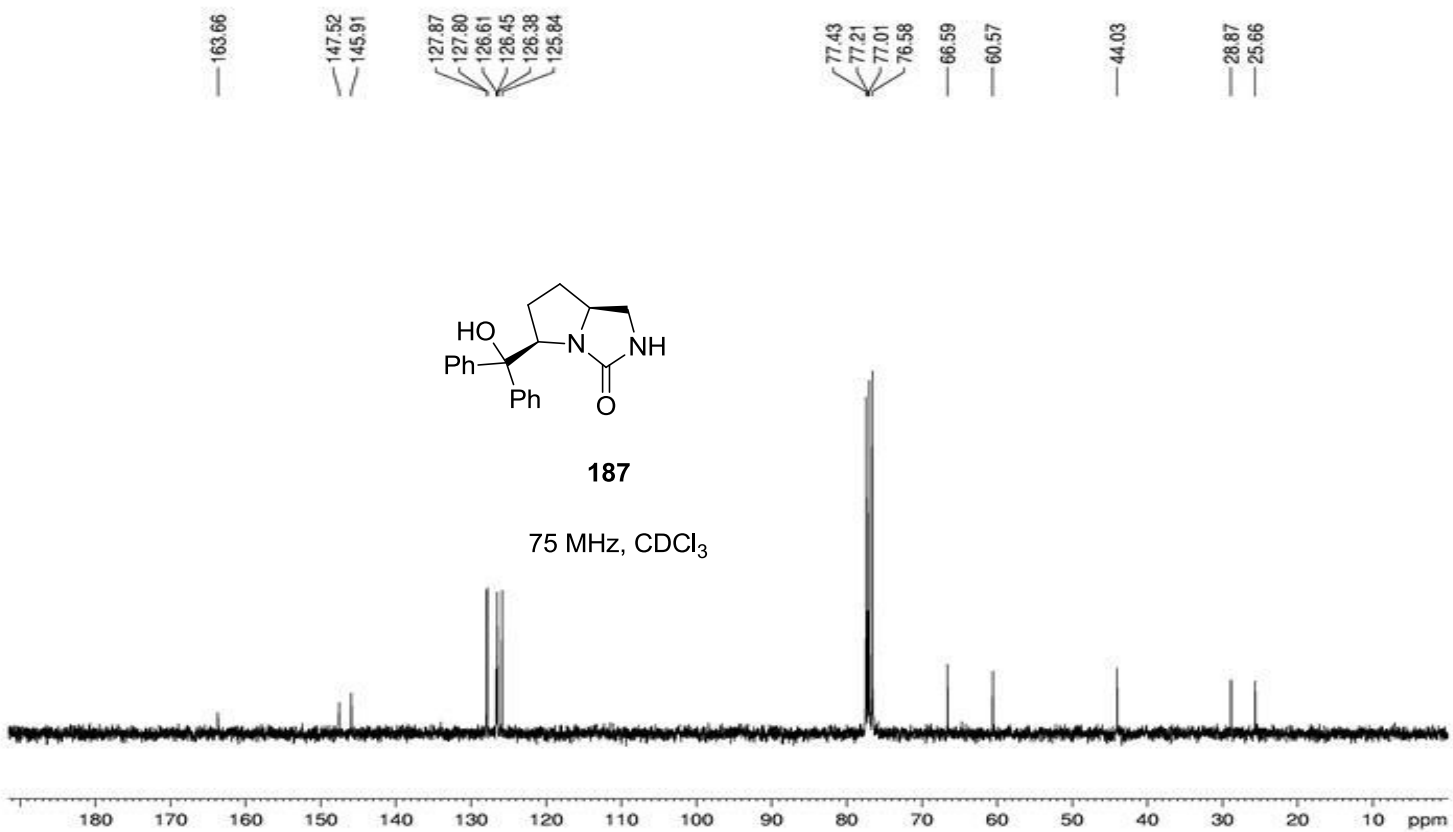


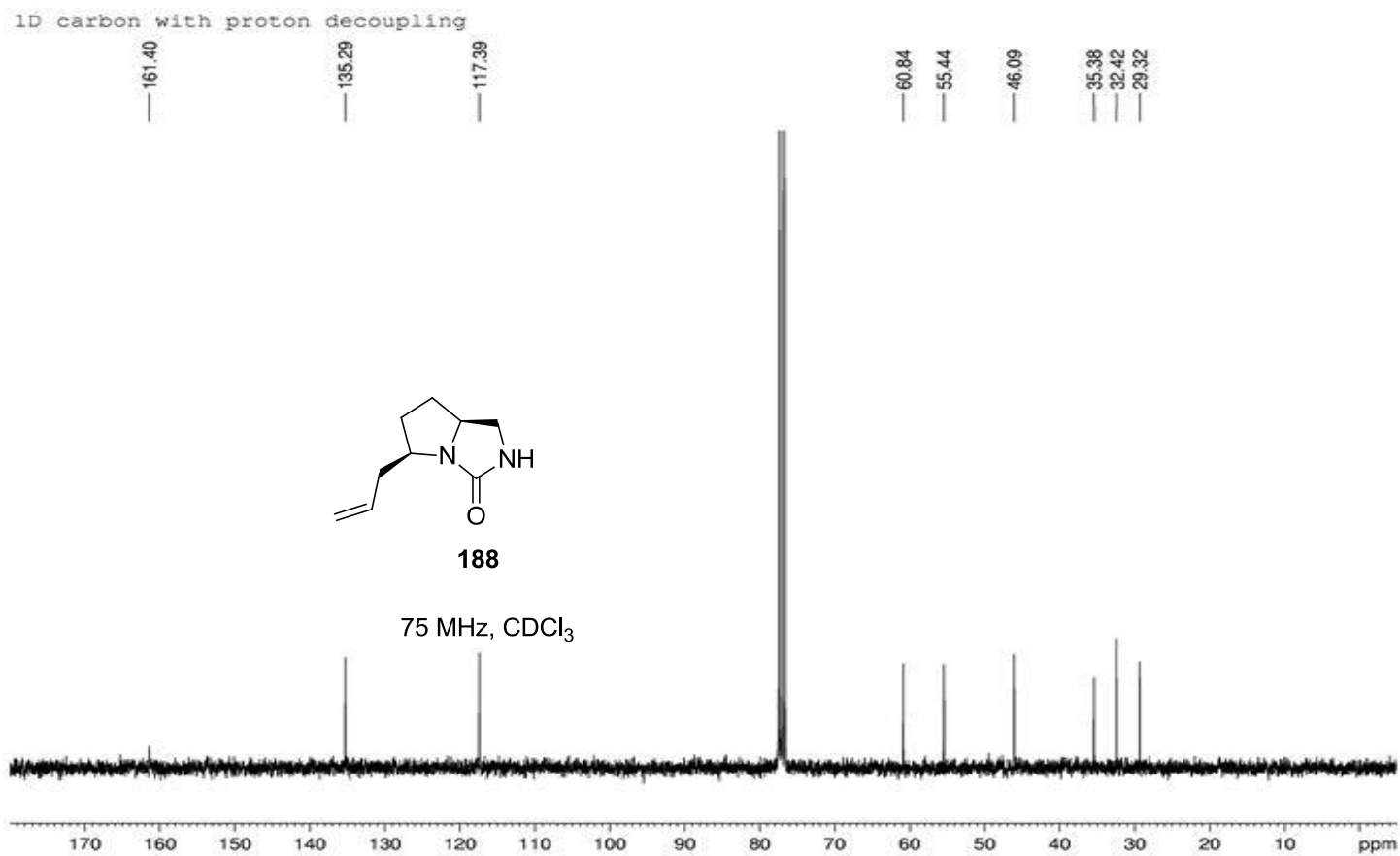
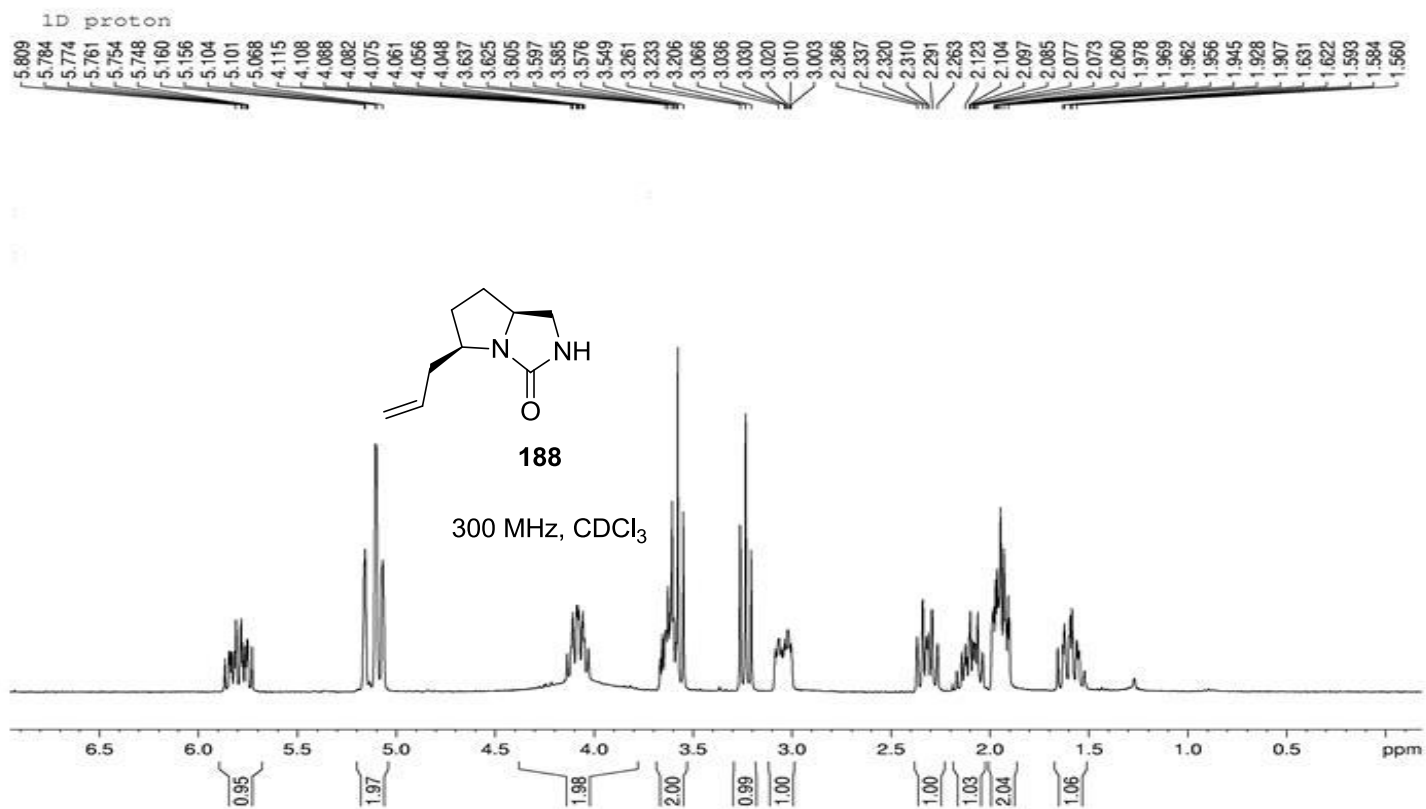
150MHz. CDCl₃

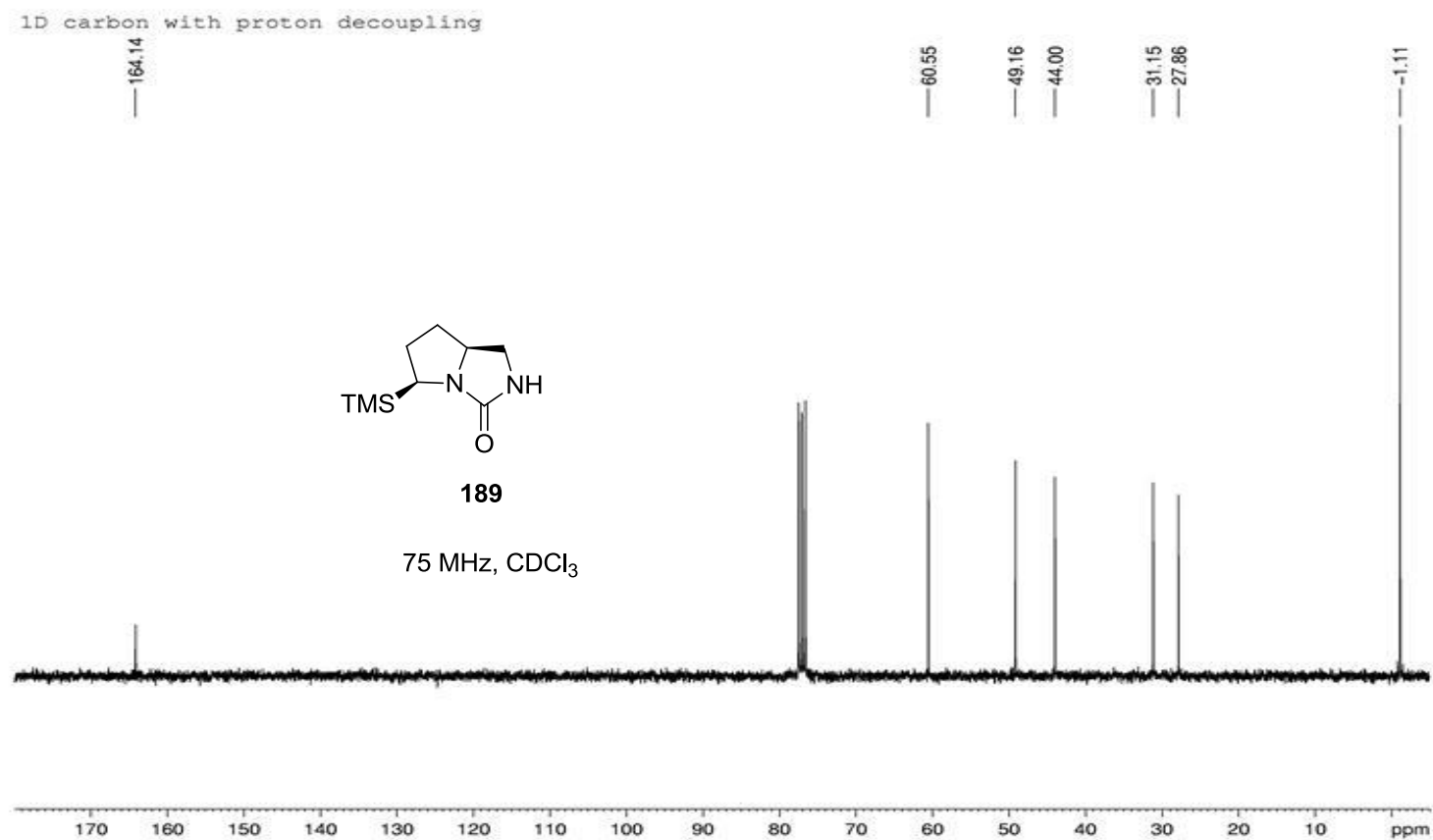
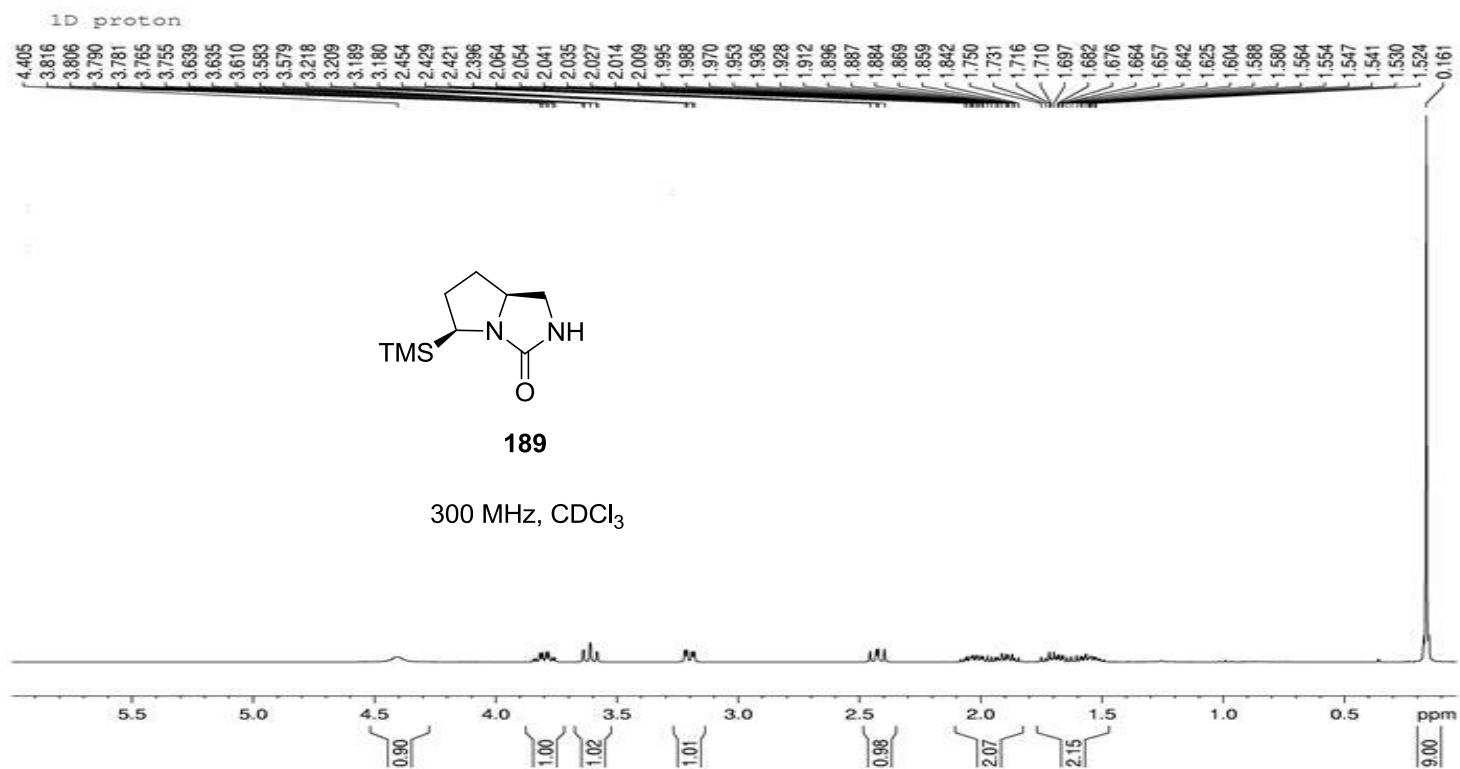




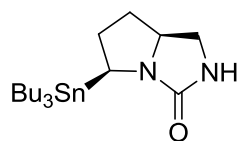
1D carbon with proton decoupling





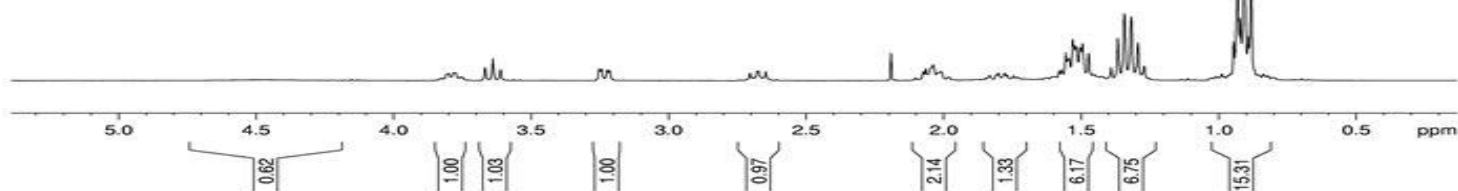


1D proton



190

300 MHz, CDCl₃



1D carbon with proton decoupling

165.83

59.72

44.40

43.32

31.46

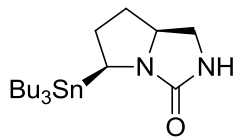
29.72

29.30

27.54

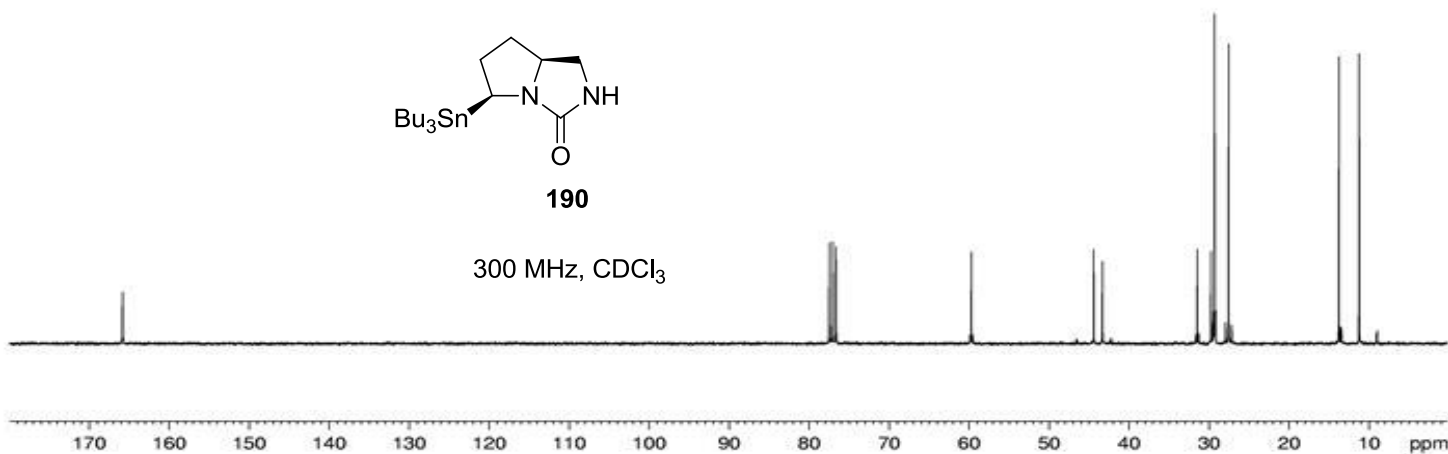
13.75

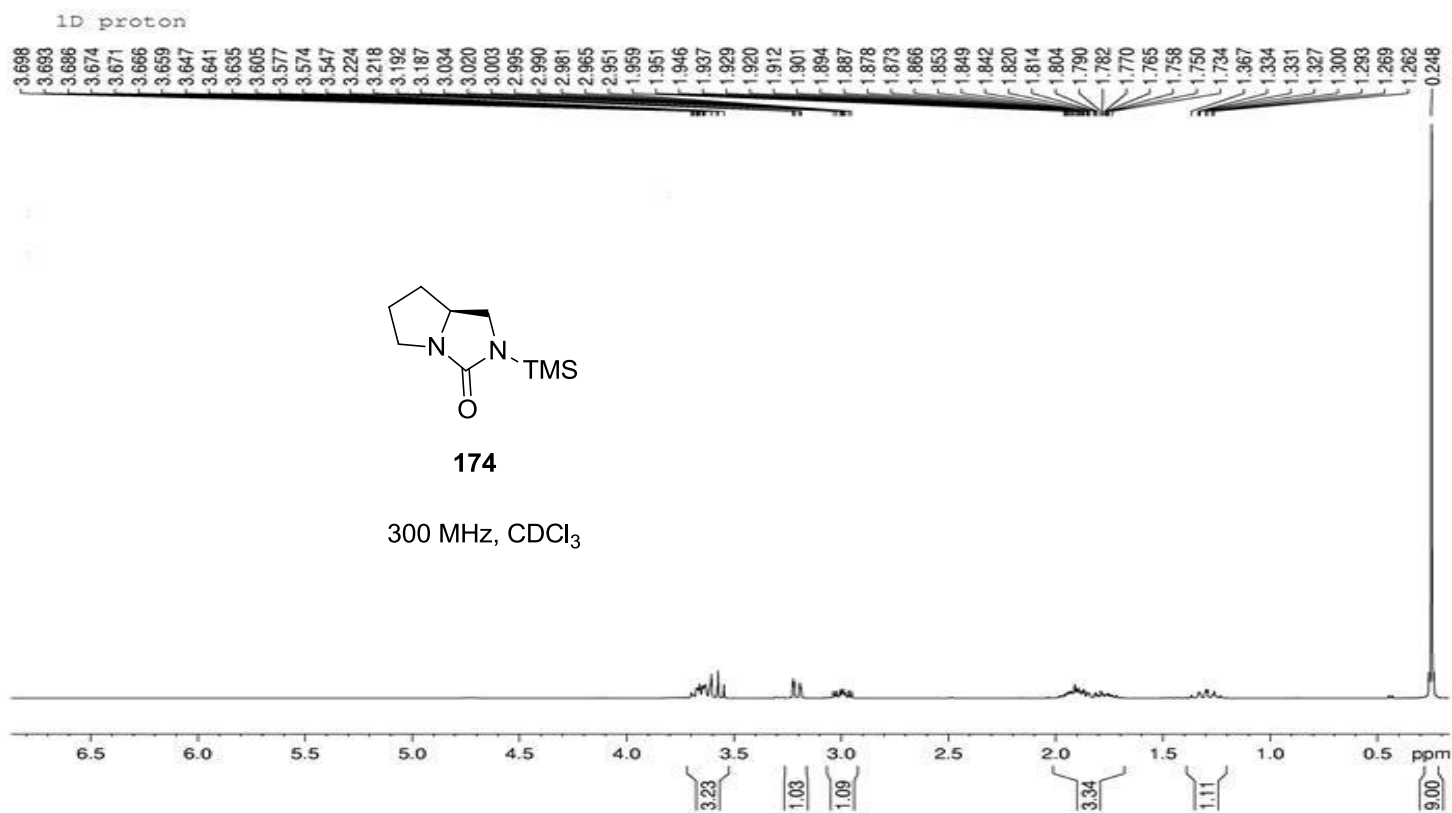
11.22



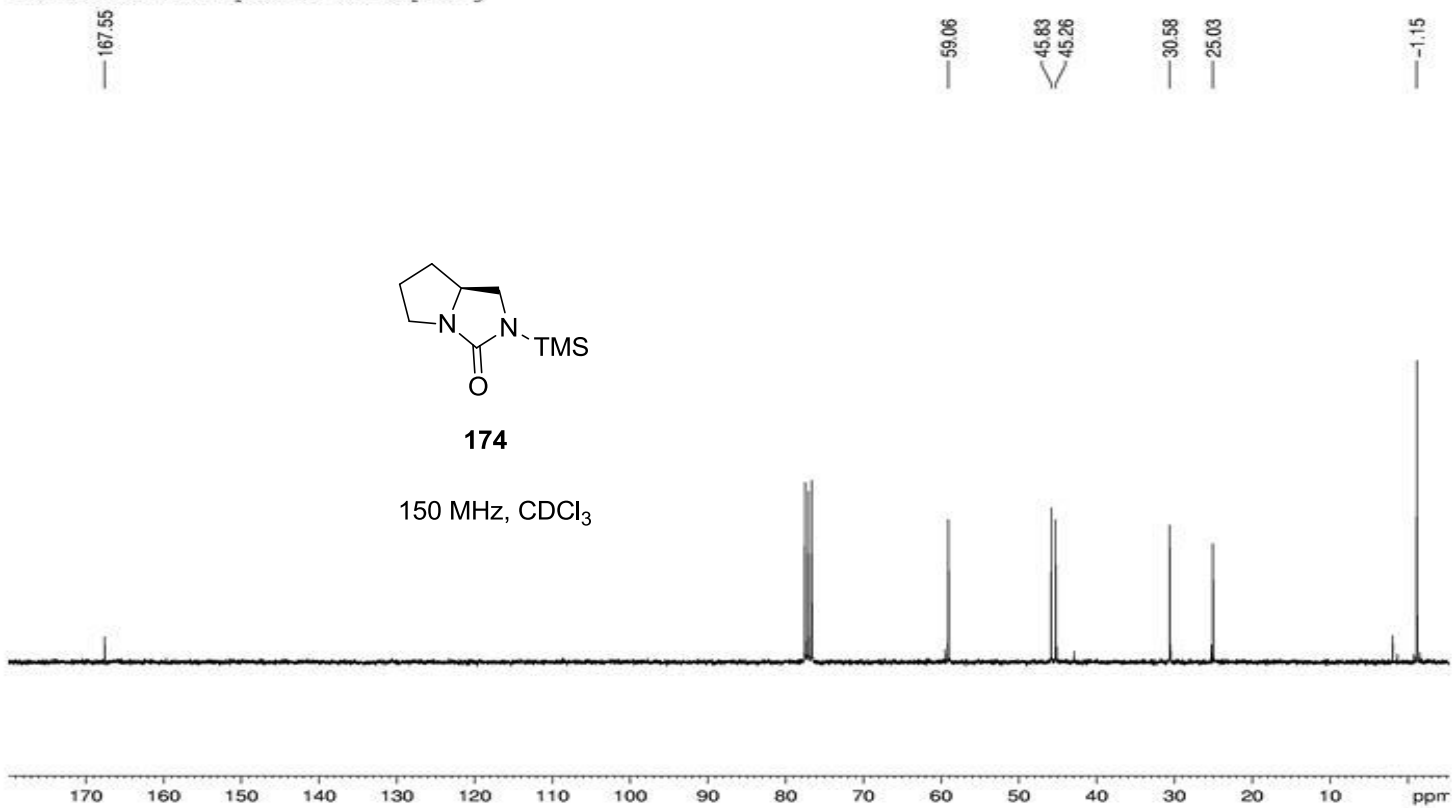
190

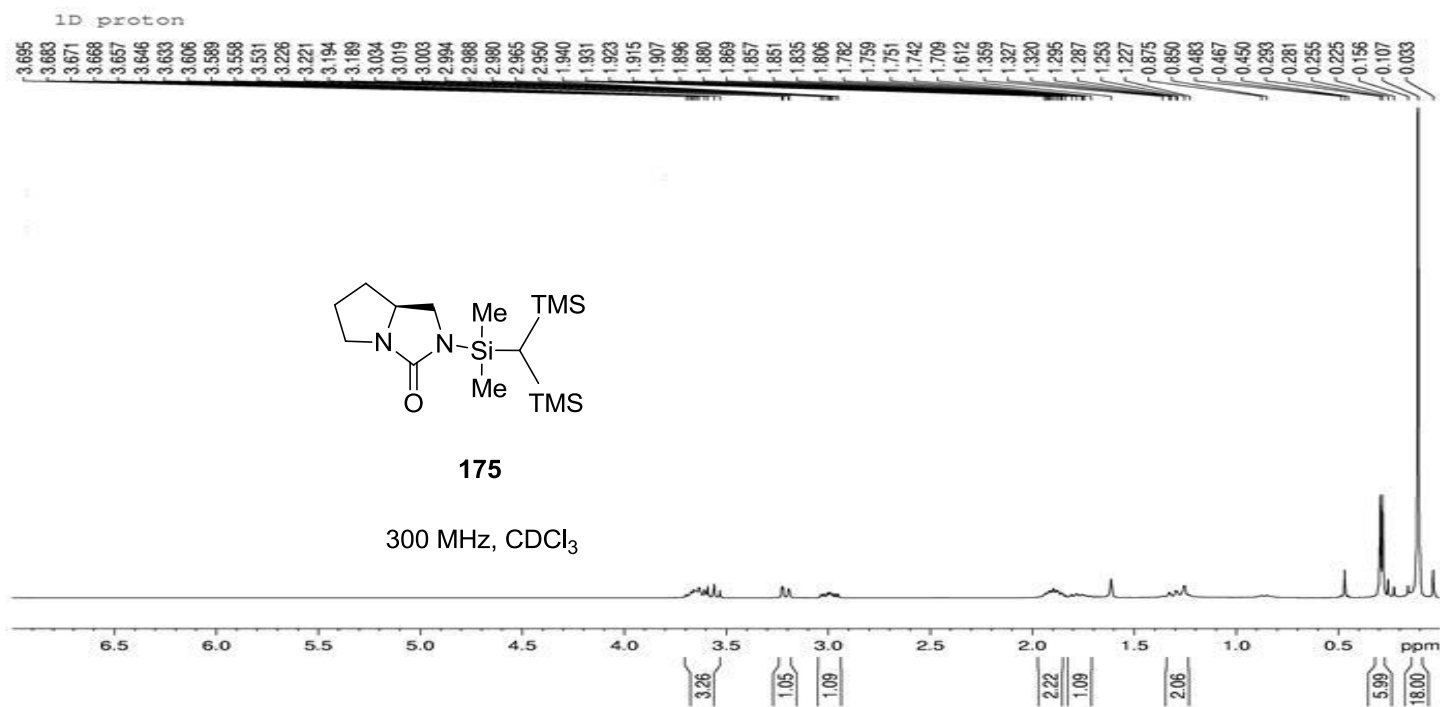
300 MHz, CDCl₃



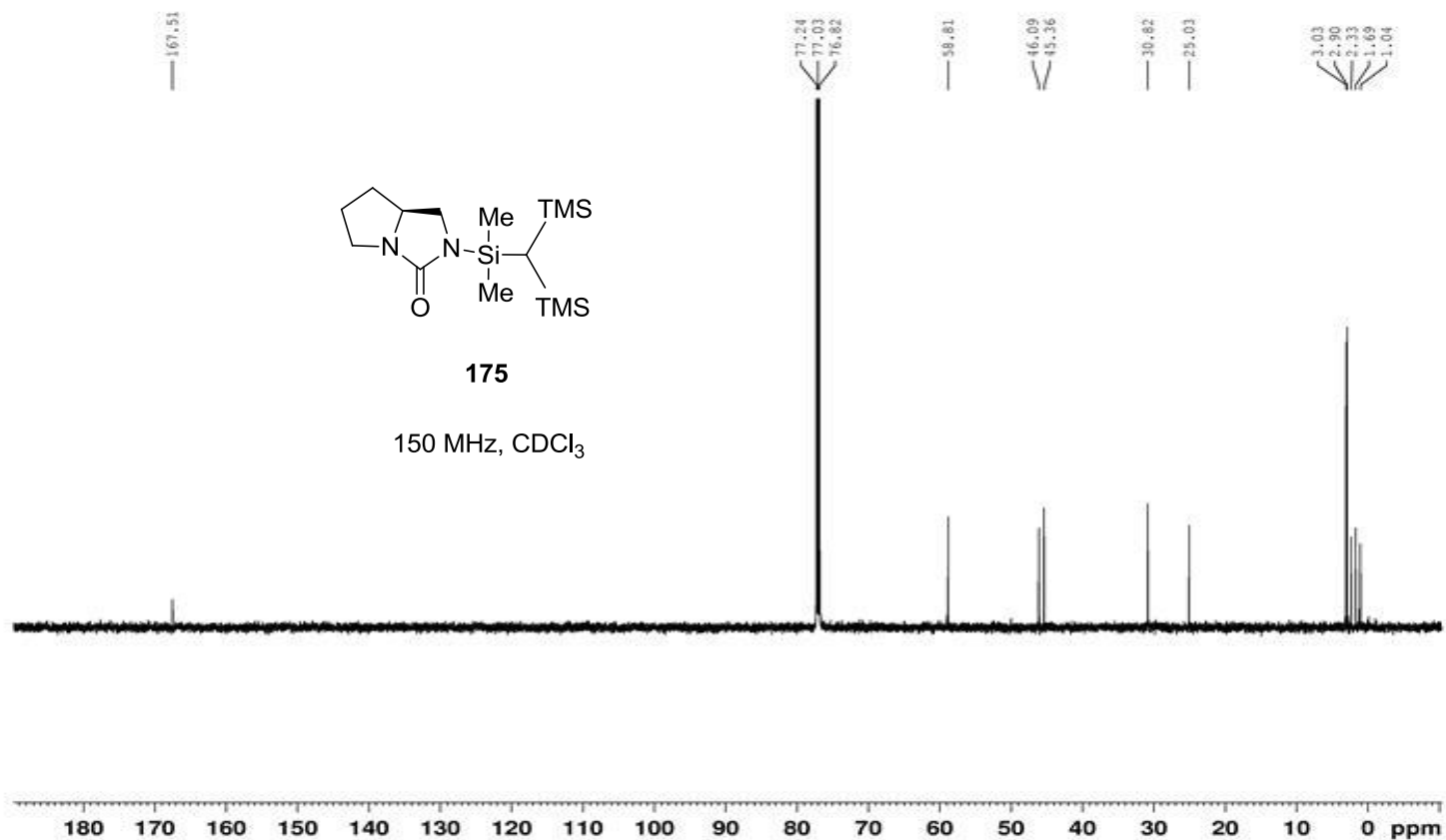


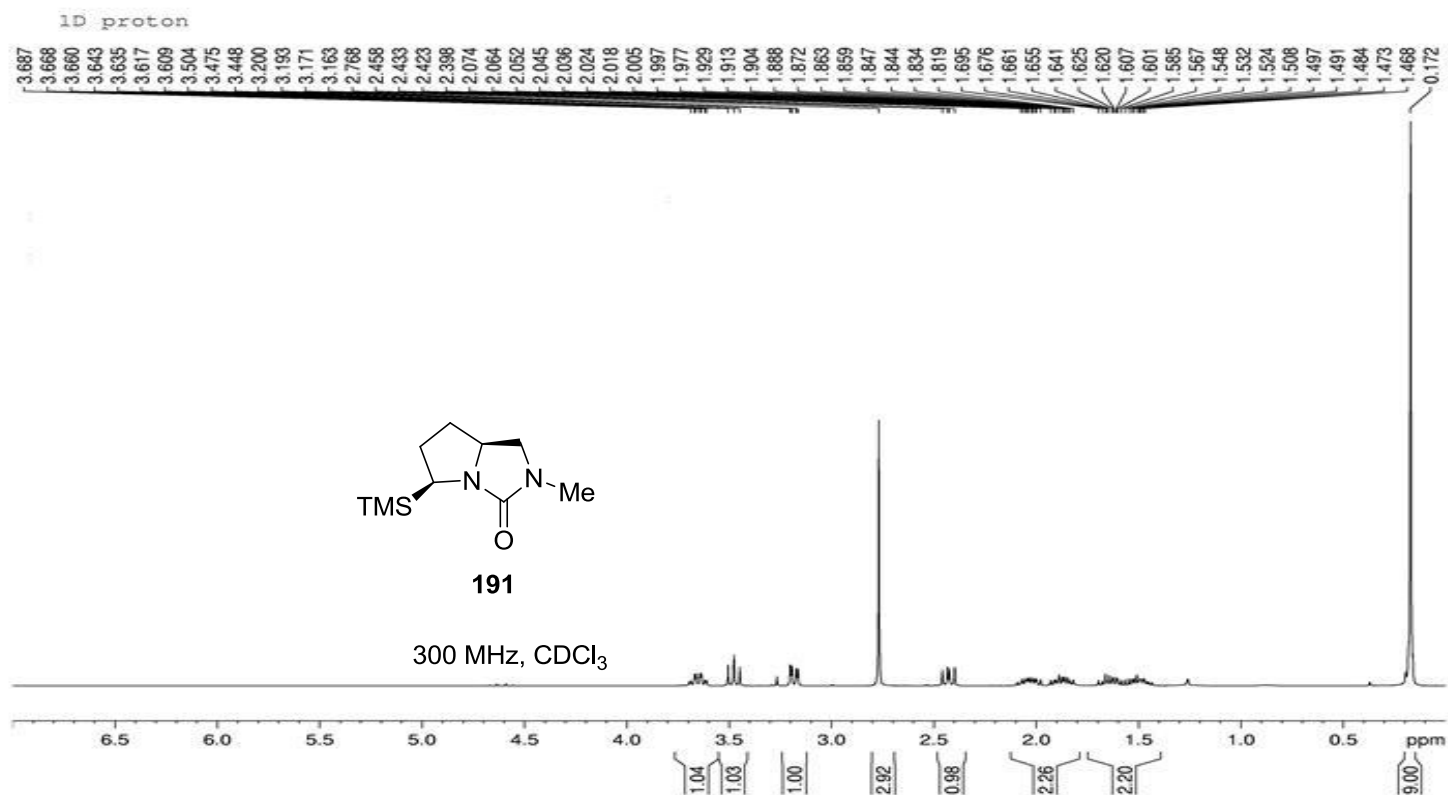
1D carbon with proton decoupling



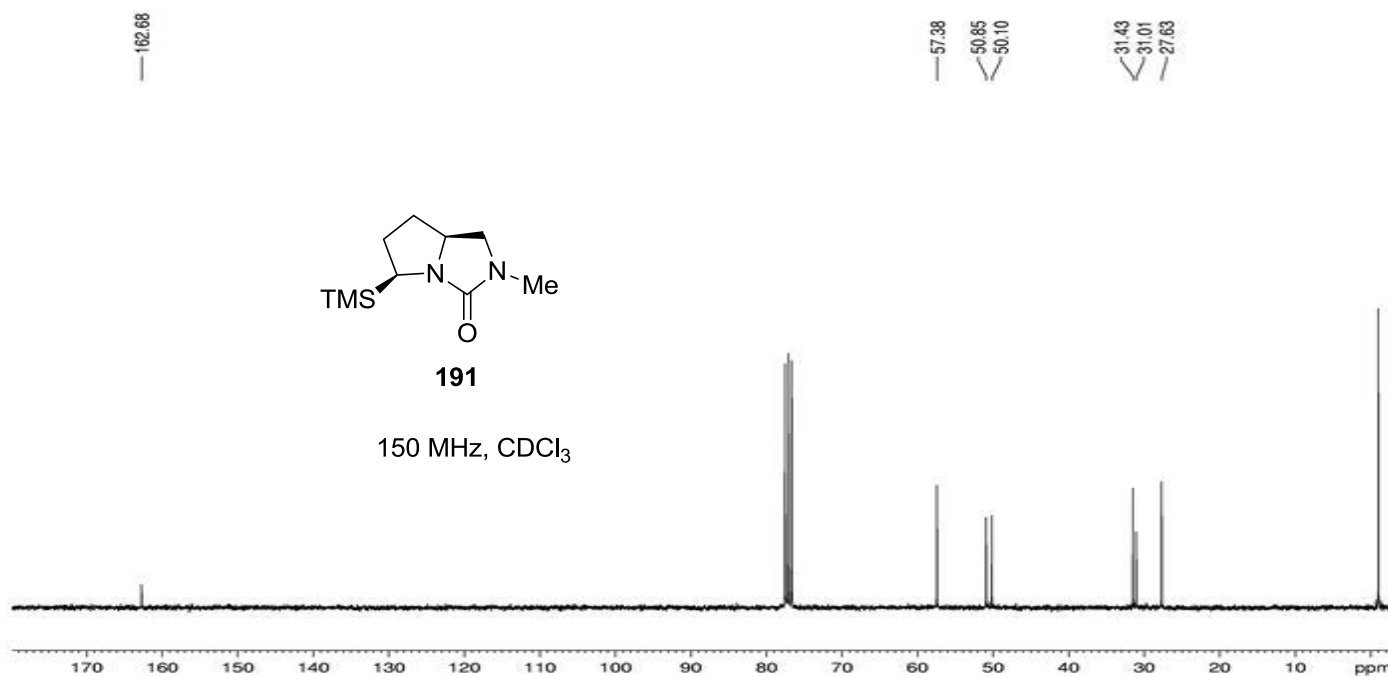


1d carbon with proton decoupling

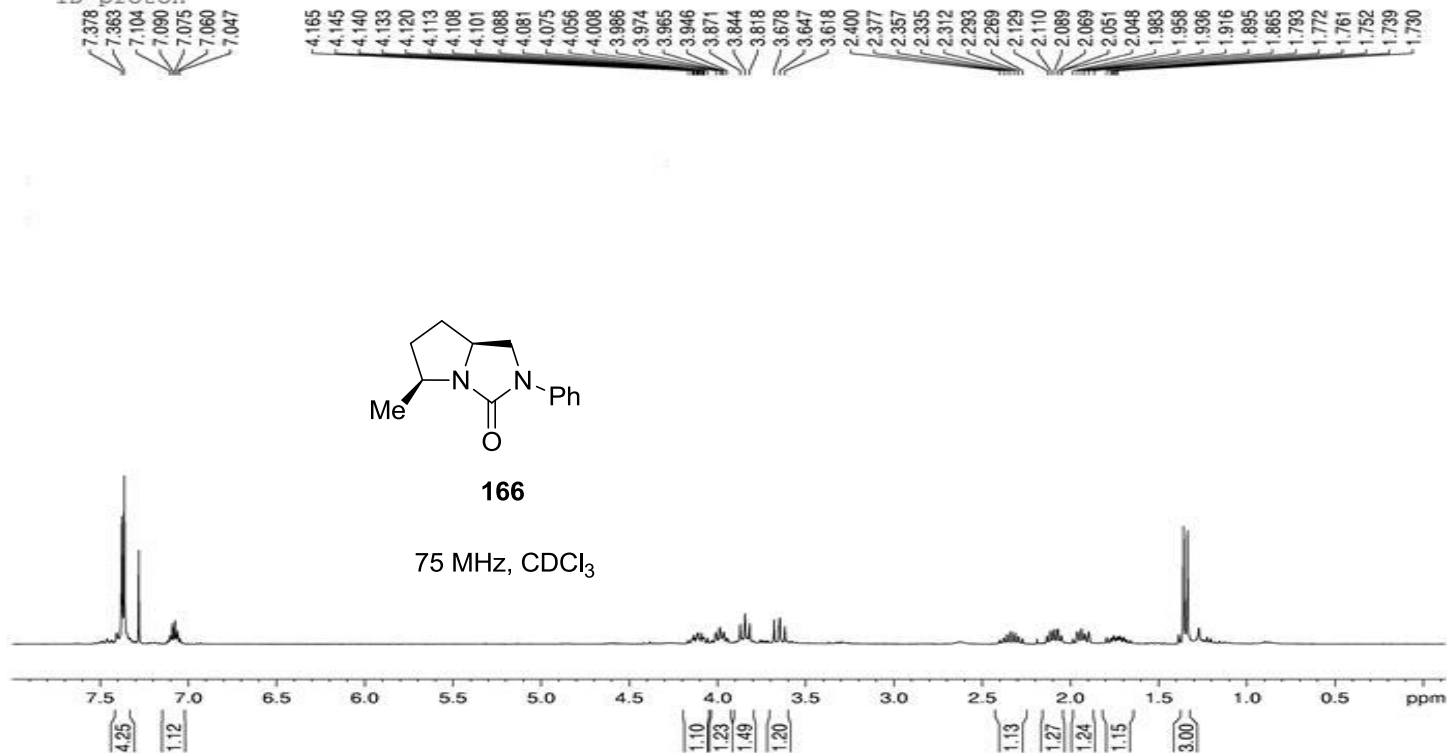




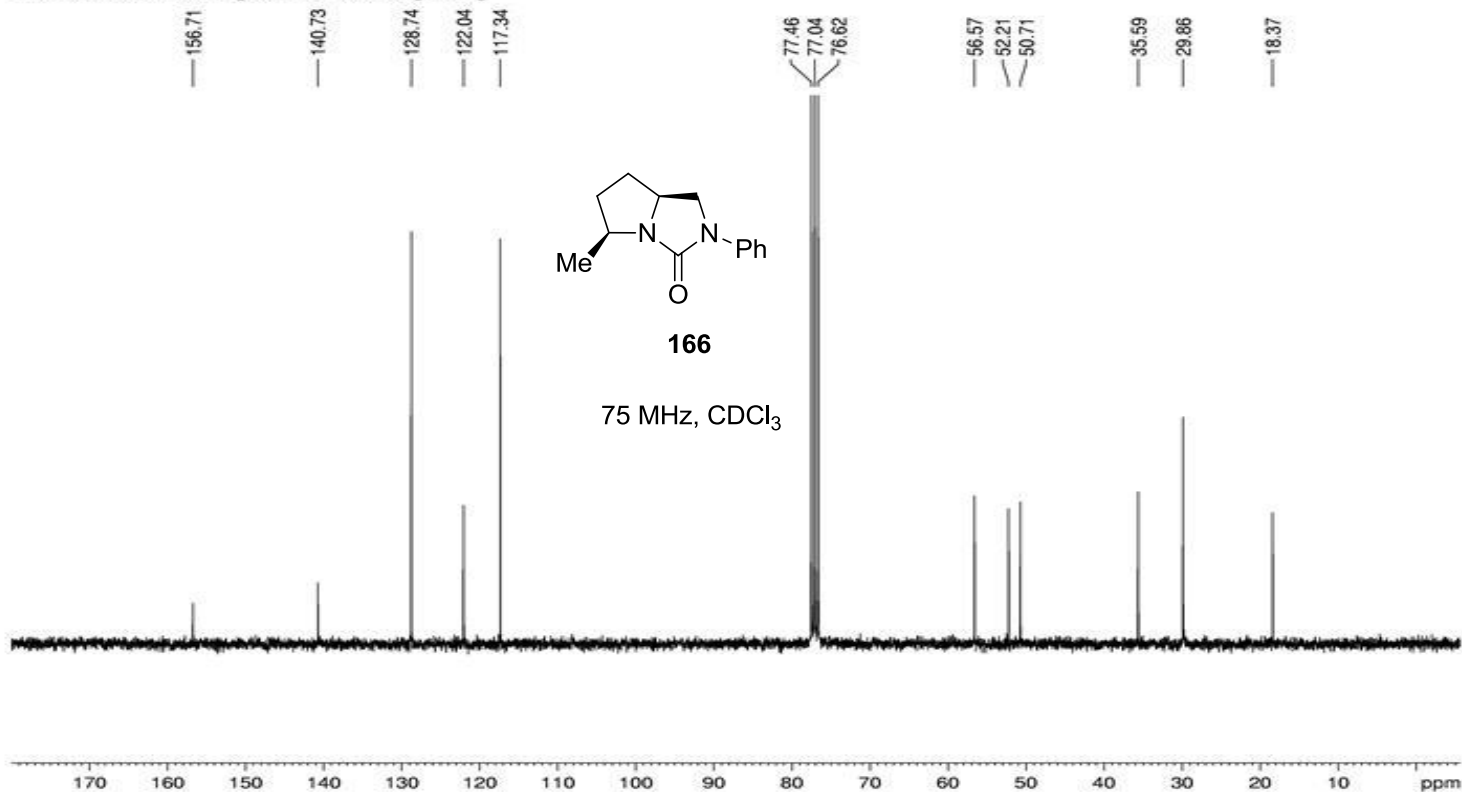
1D carbon with proton decoupling

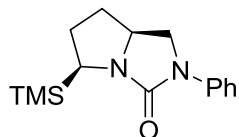


1D proton



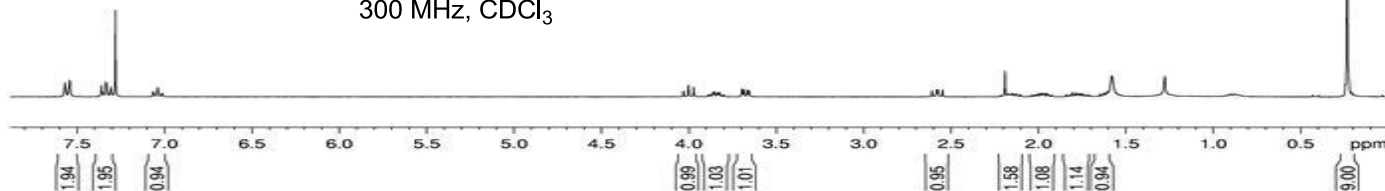
1D carbon with proton decoupling



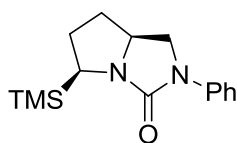


194

300 MHz, CDCl₃

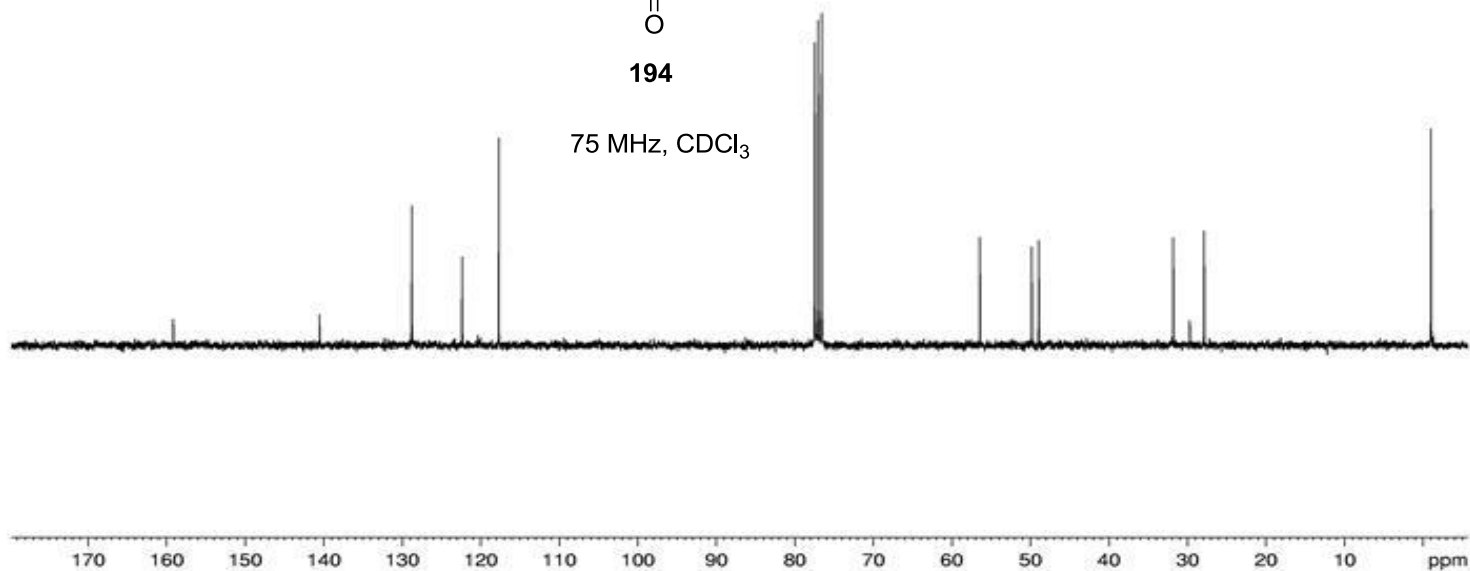


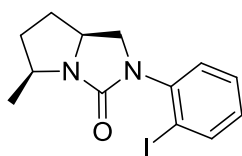
1D carbon with proton decoupling



194

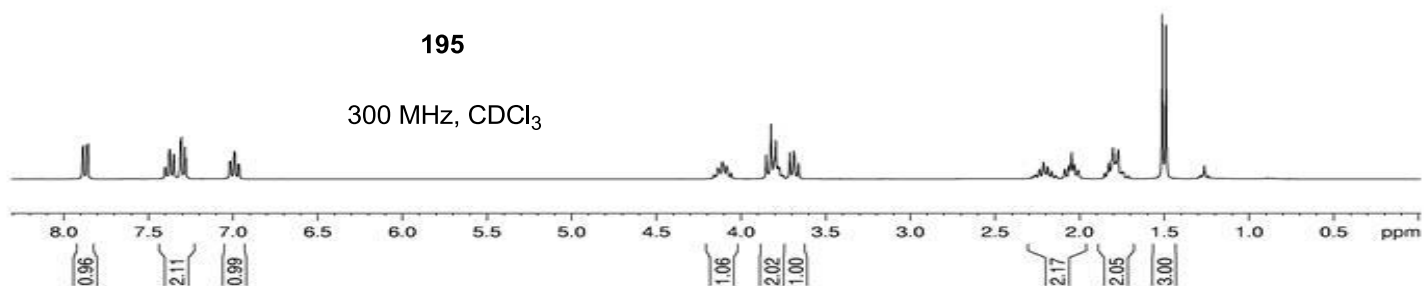
75 MHz, CDCl₃



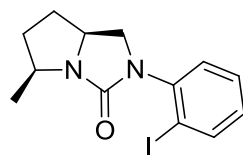


195

300 MHz, CDCl₃

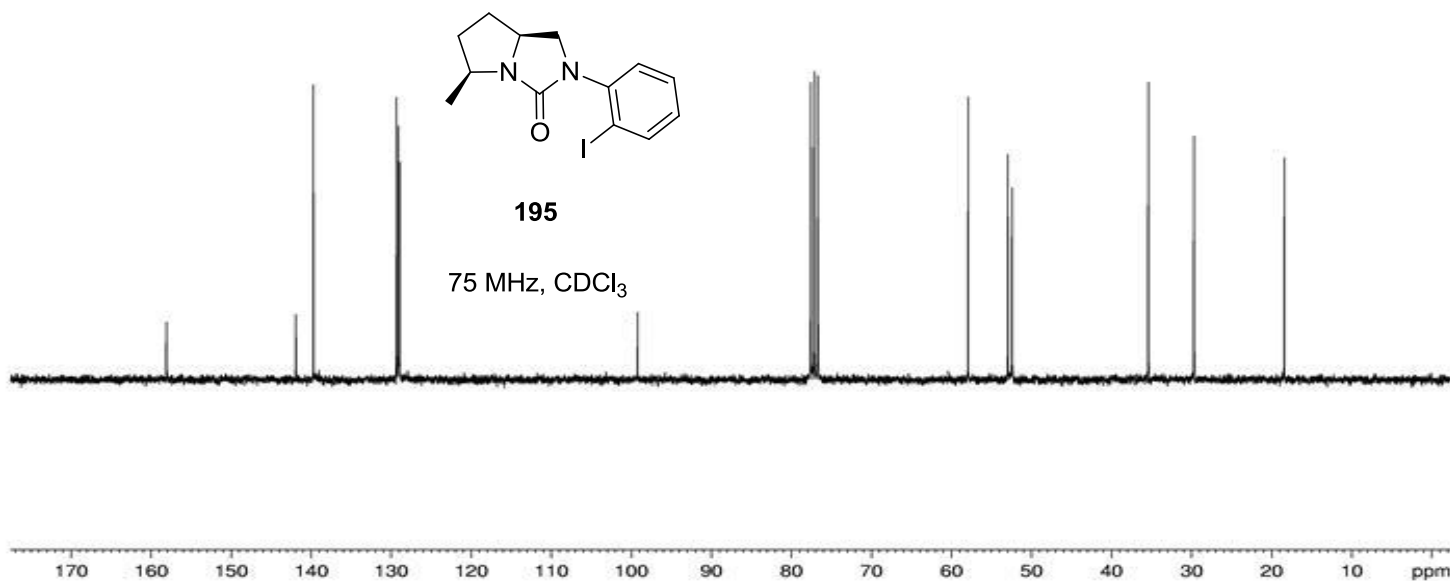


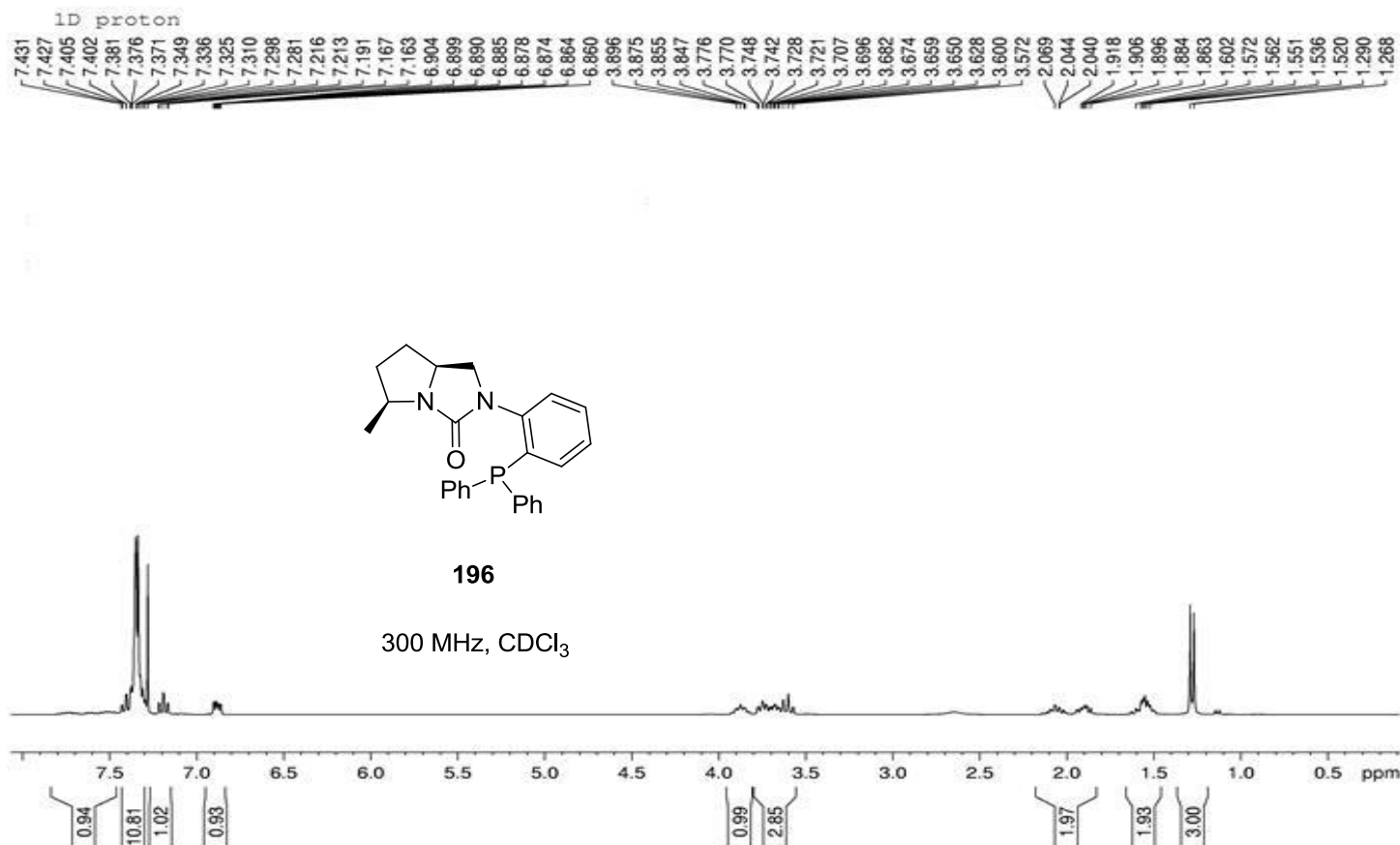
1D carbon with proton decoupling



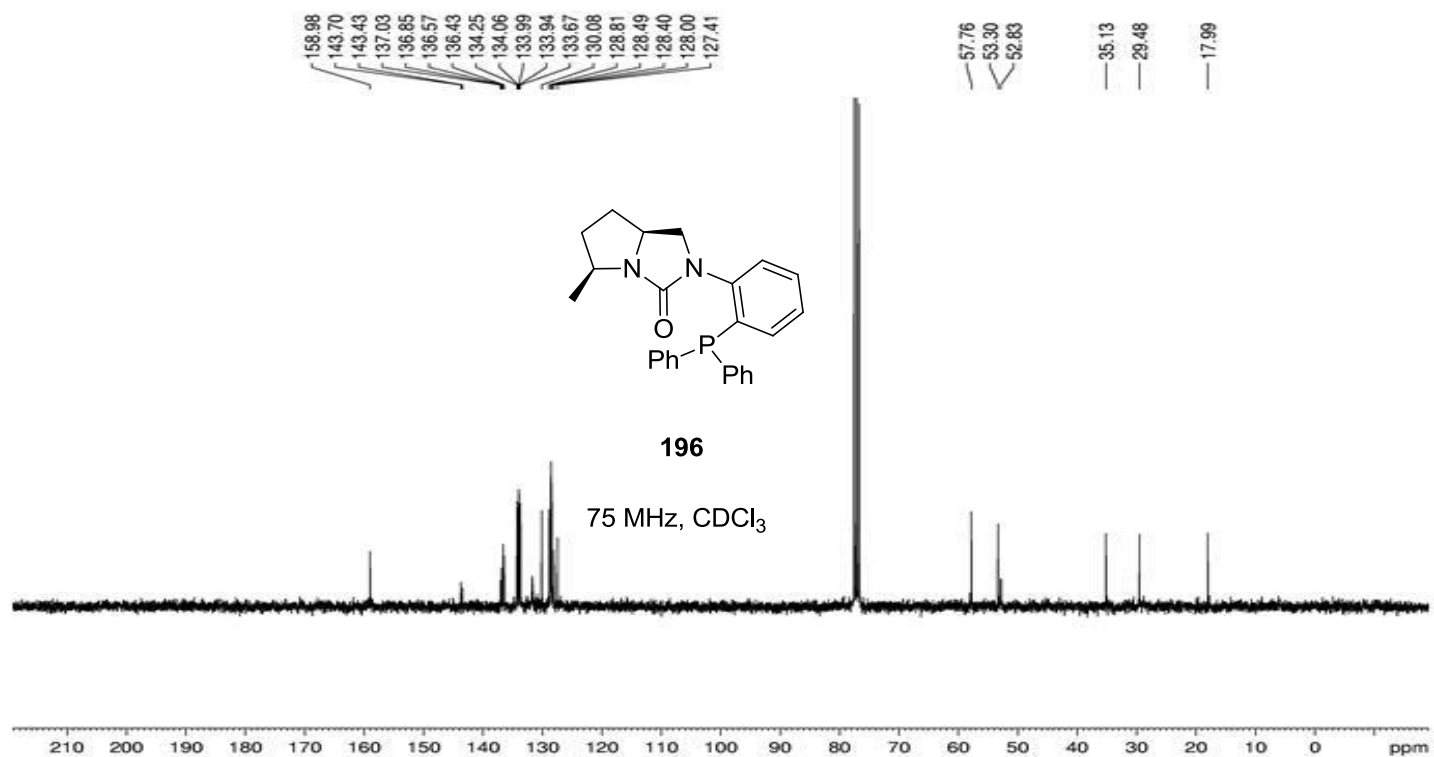
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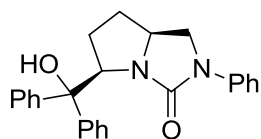
75 MHz, CDCl₃





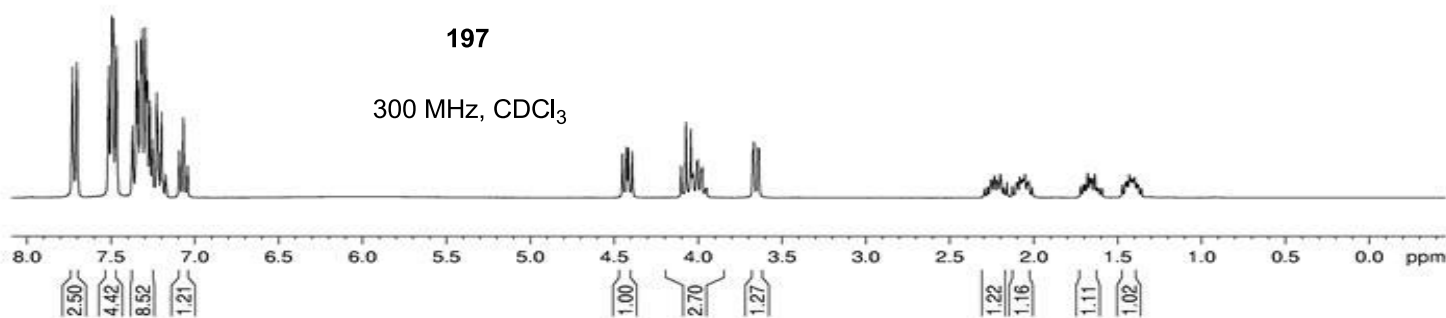
1D carbon with proton decoupling



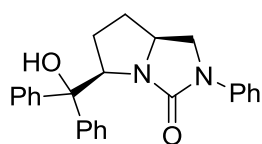


197

300 MHz, CDCl₃

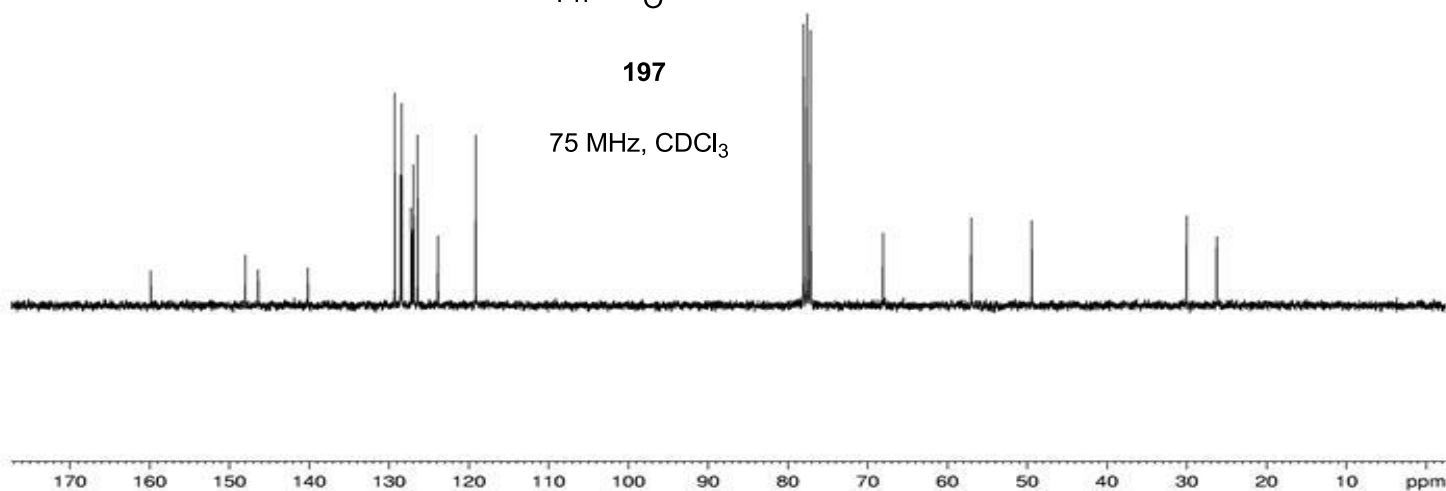


1D carbon with proton decoupling

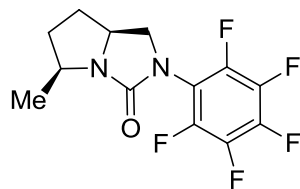
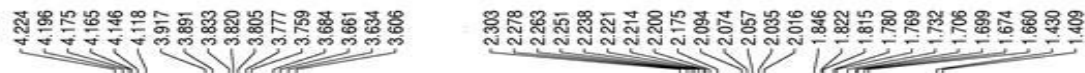


197

75 MHz, CDCl₃

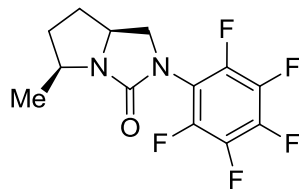
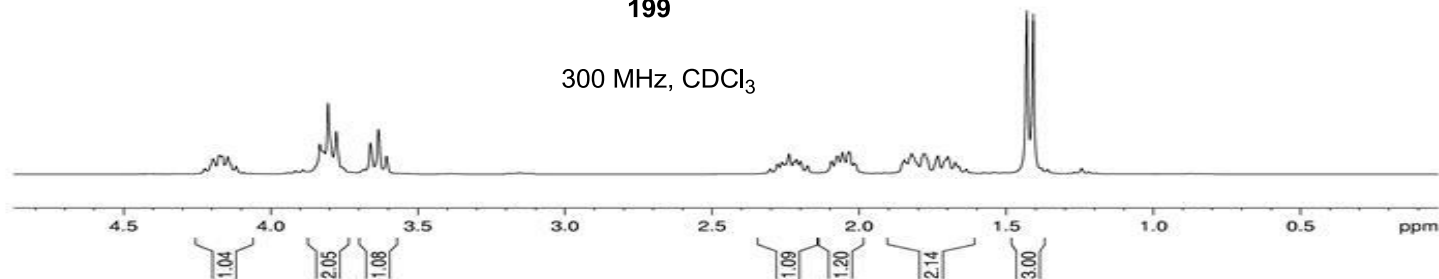


1D proton



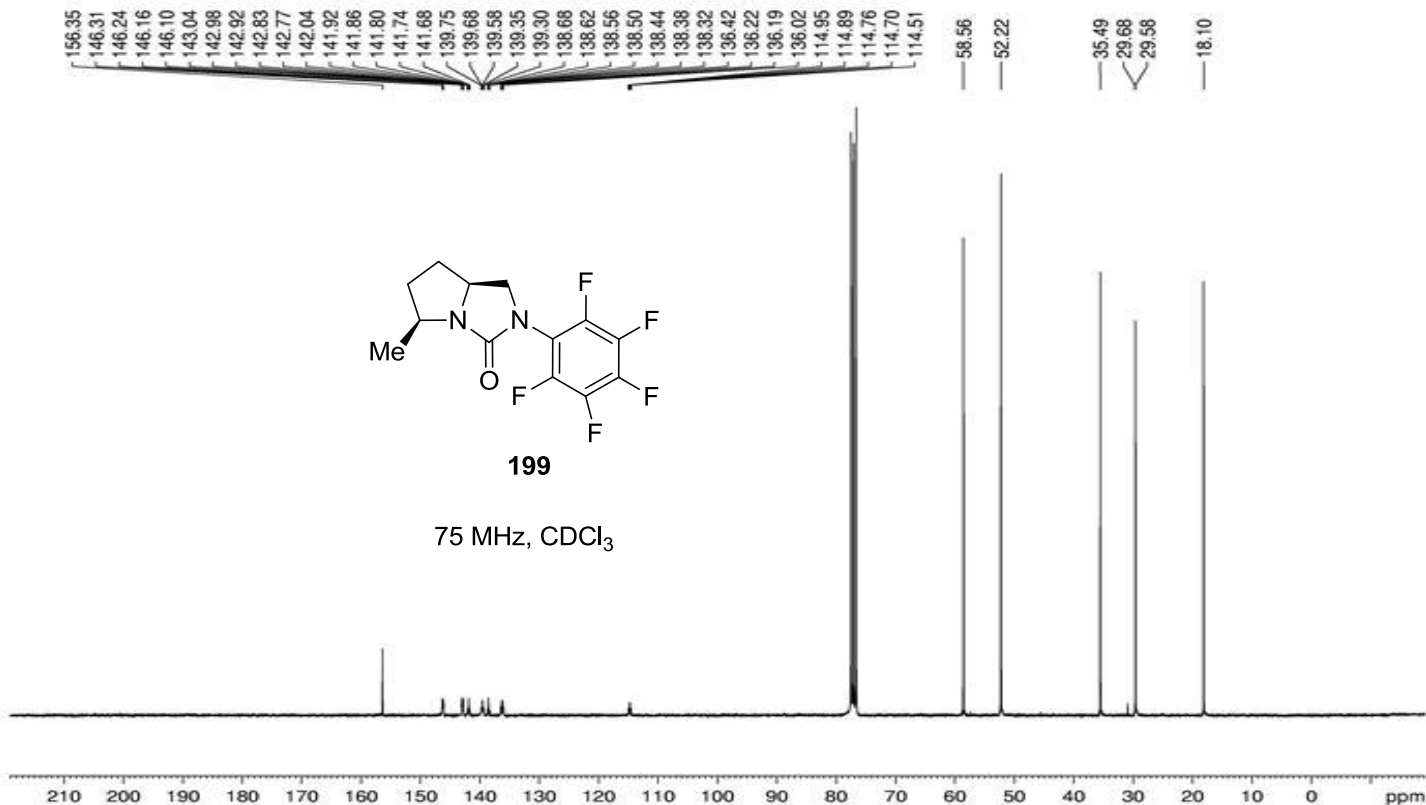
199

300 MHz, CDCl₃



199

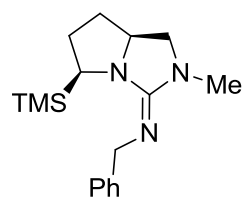
75 MHz, CDCl₃



1d
proton
7.308
7.295
7.285
7.273
7.260
7.171
7.159
7.147

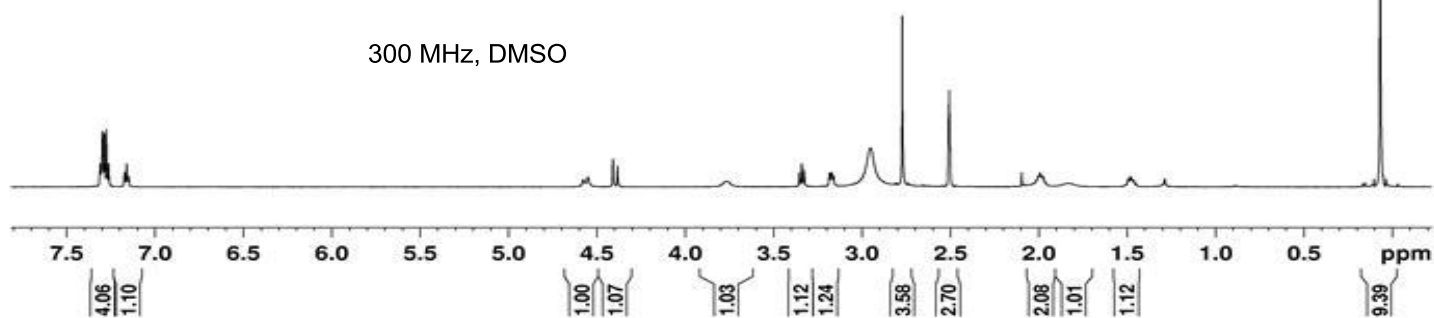
4.576
4.551
4.410
4.383
3.763
3.354
3.340
3.326
3.184
3.175
3.170
3.160
2.953
2.884
2.807
2.772
2.747
2.738
2.512
2.509
2.506
2.503
2.500
2.096
2.002
1.992
1.985
1.980
1.972
1.960
1.829
1.495
1.488
1.481
1.474
1.468
1.461
1.448
1.286

0.068



202

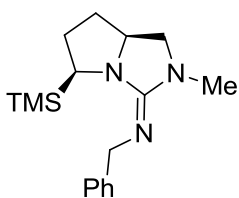
300 MHz, DMSO



1d carbon with proton decoupling

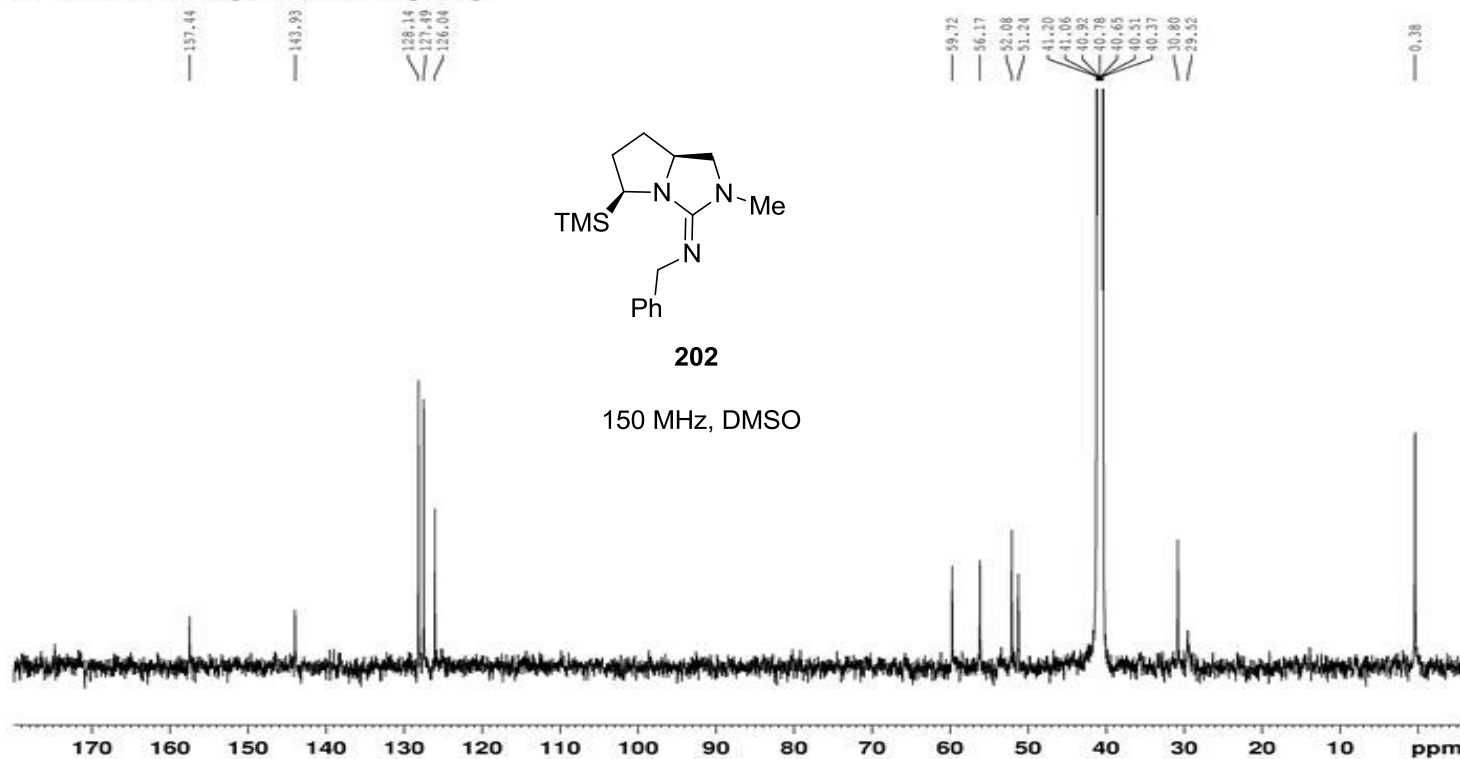
157.44
143.93

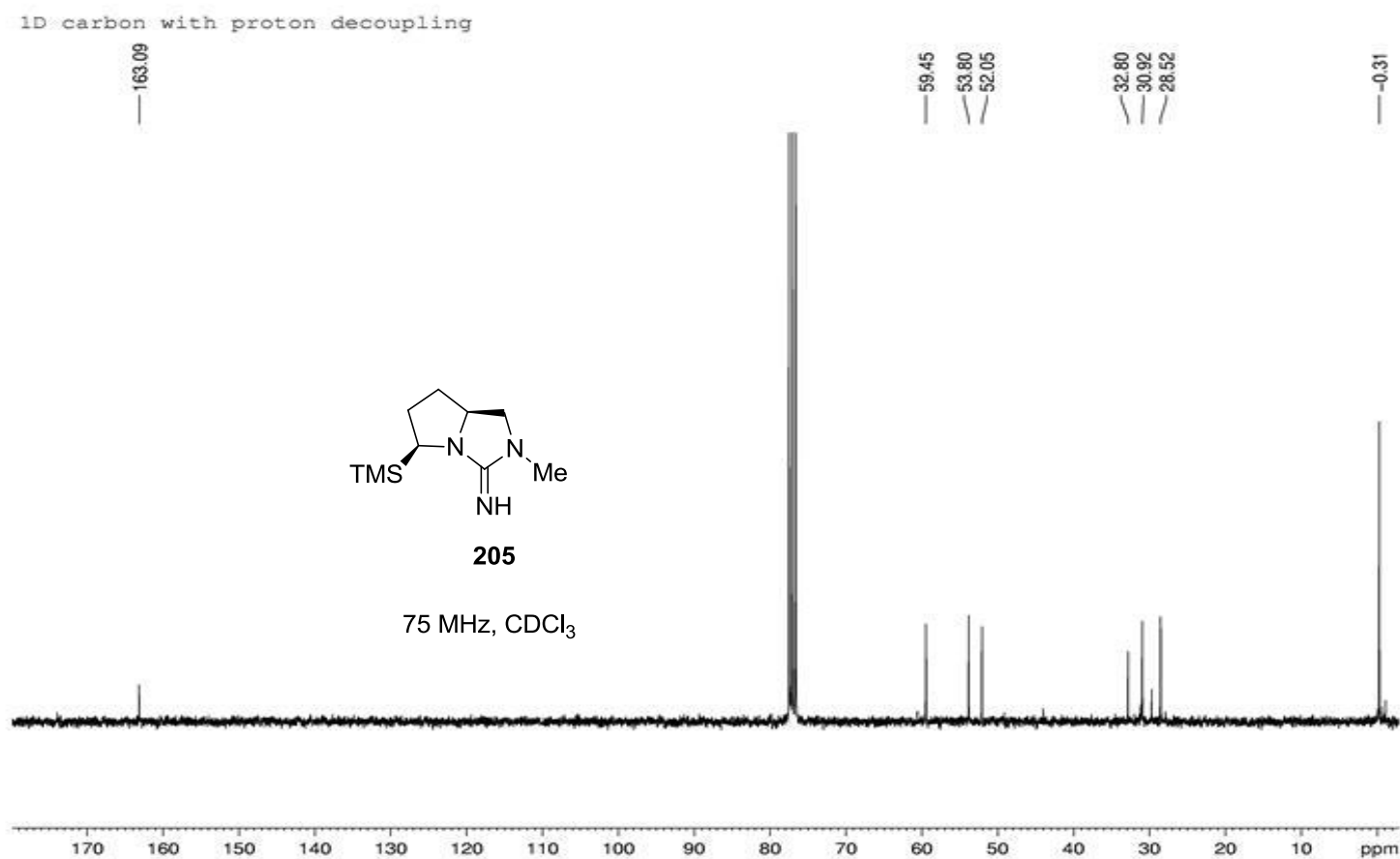
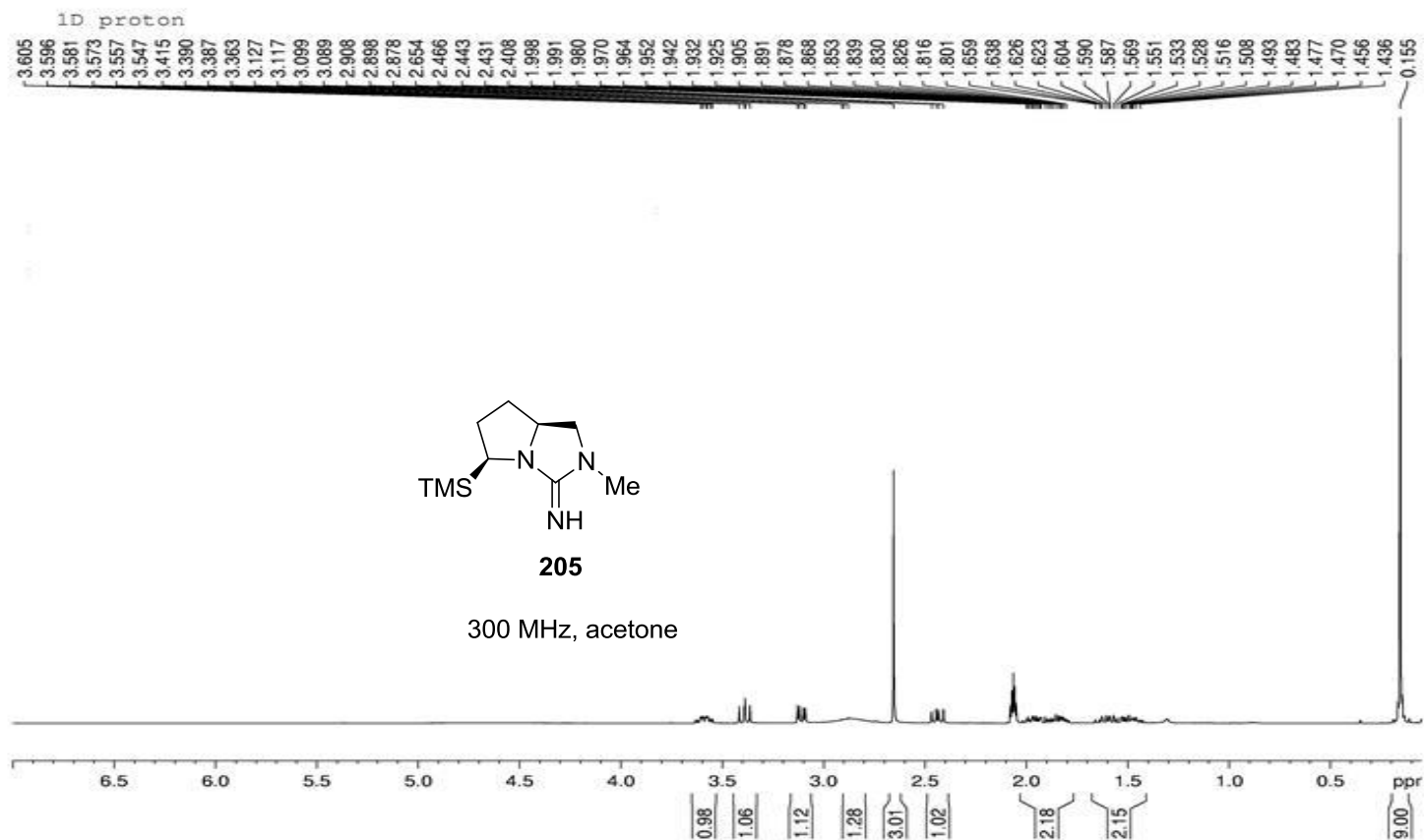
128.14
127.49
126.04



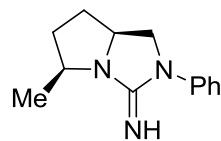
202

150 MHz, DMSO



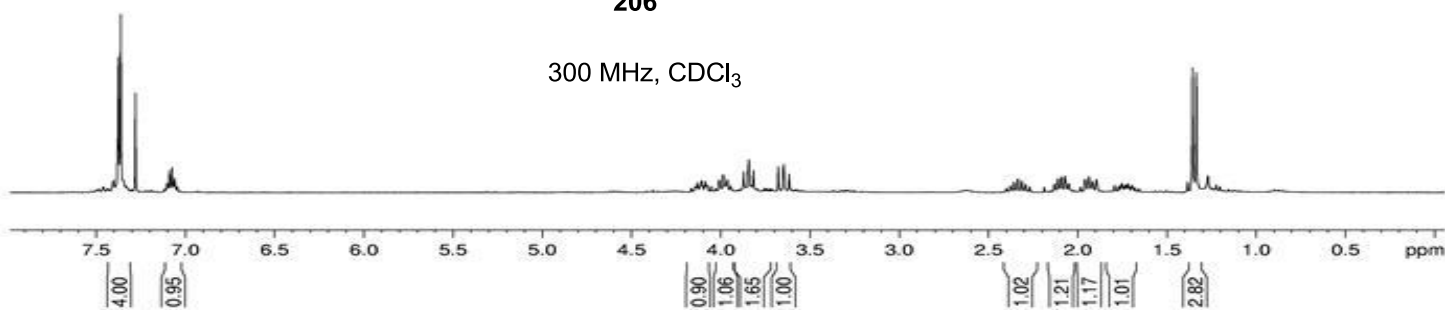


7.378 1D
7.363
7.104
7.090
7.075
7.060
7.047
4.165
4.145
4.140
4.133
4.120
4.113
4.108
4.101
4.088
4.081
4.075
4.056
4.008
3.986
3.974
3.965
3.946
3.871
3.844
3.818
3.678
3.647
3.618
2.400
2.377
2.357
2.335
2.312
2.293
2.269
2.129
2.110
2.089
2.069
2.051
2.048
1.983
1.958
1.936
1.916
1.895
1.793
1.772
1.761
1.752
1.739
1.730
1.719
1.711
1.698
1.690
1.357
1.336



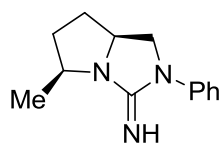
206

300 MHz, CDCl₃



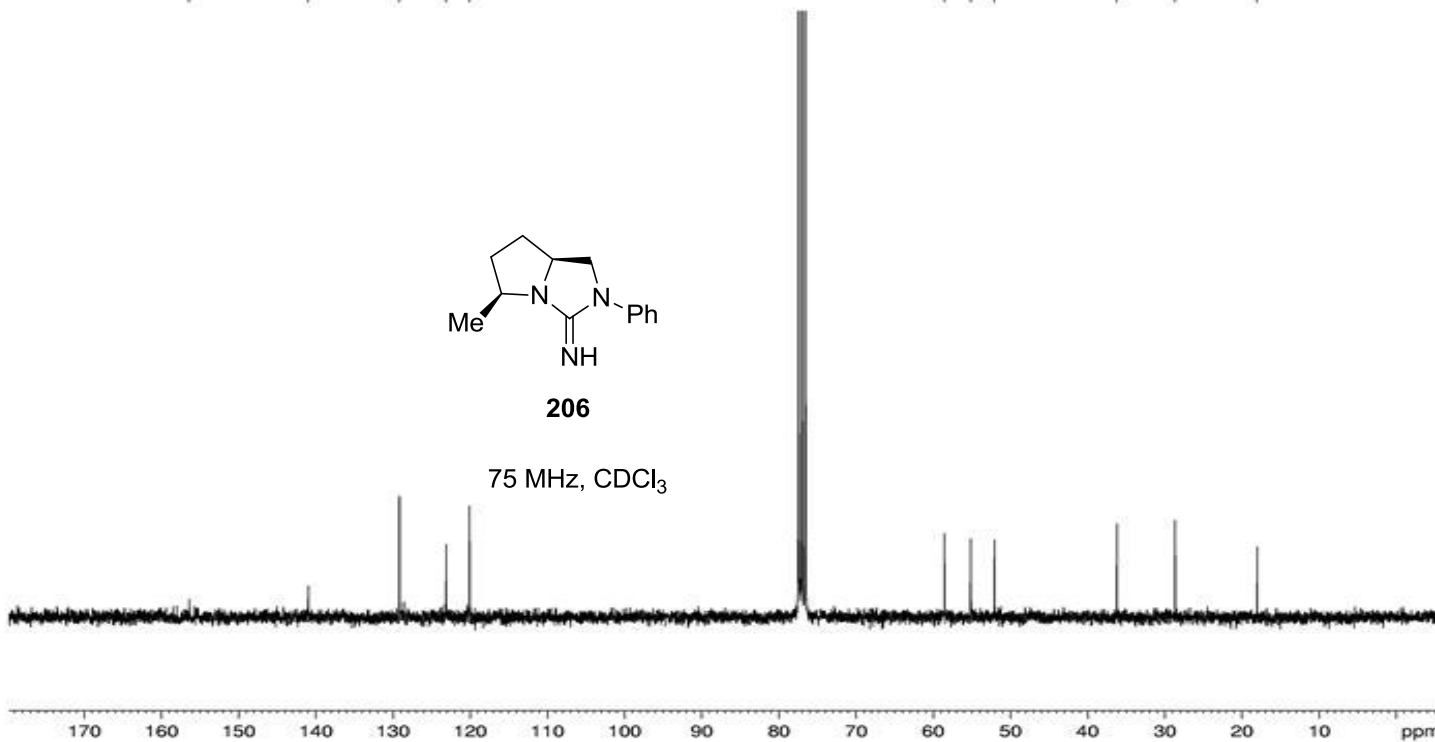
1D carbon with proton decoupling

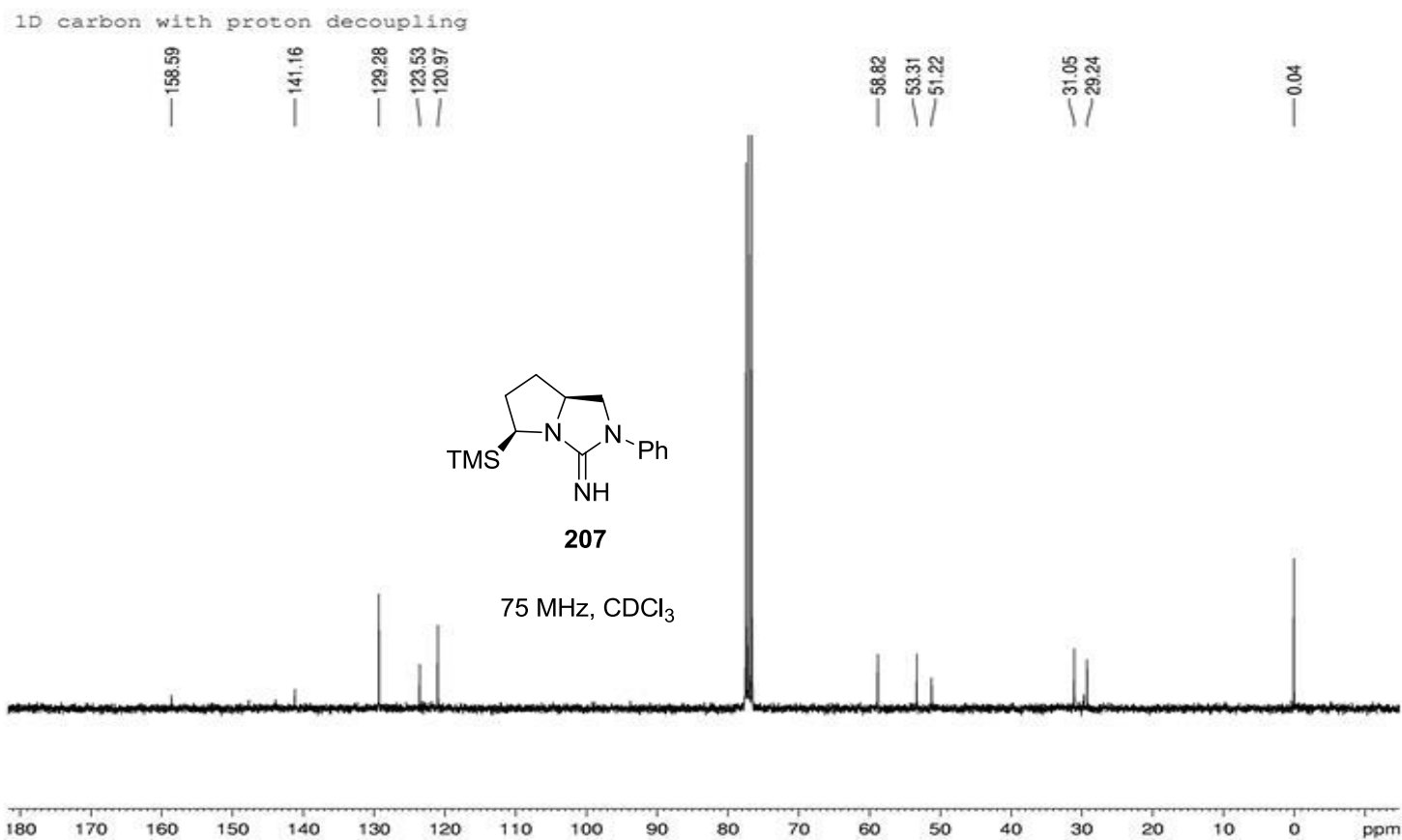
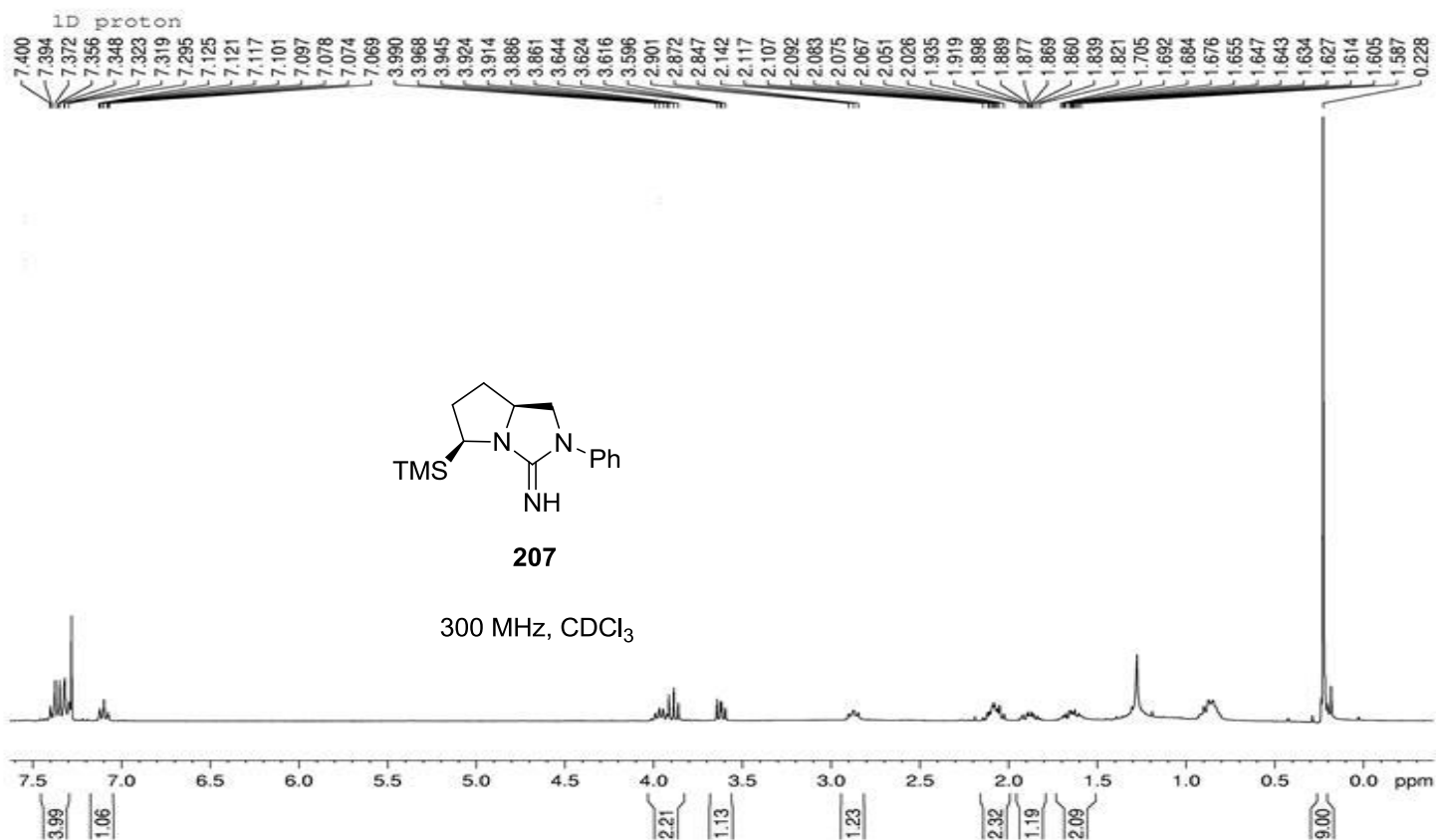
156.42 140.99 129.18 123.12 120.11 58.56 55.15 52.07 36.21 28.68 18.03



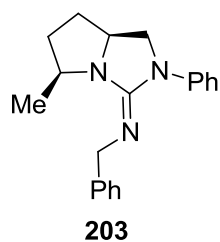
206

75 MHz, CDCl₃

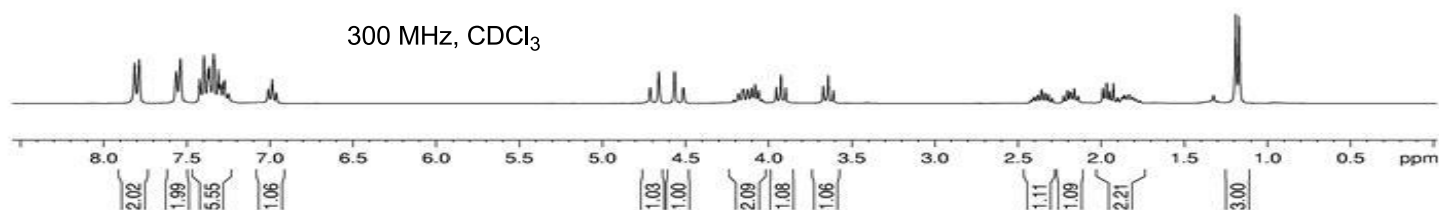




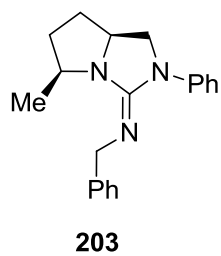
1D proton



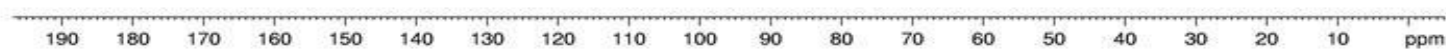
300 MHz, CDCl₃

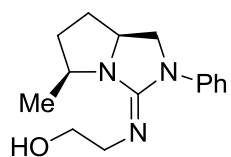
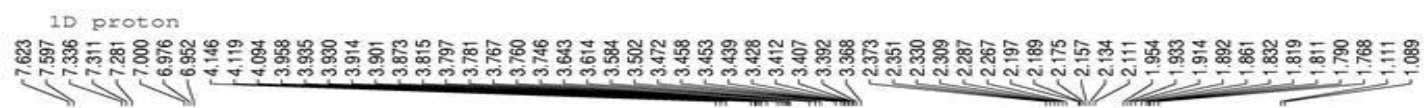


1D carbon with proton decoupling



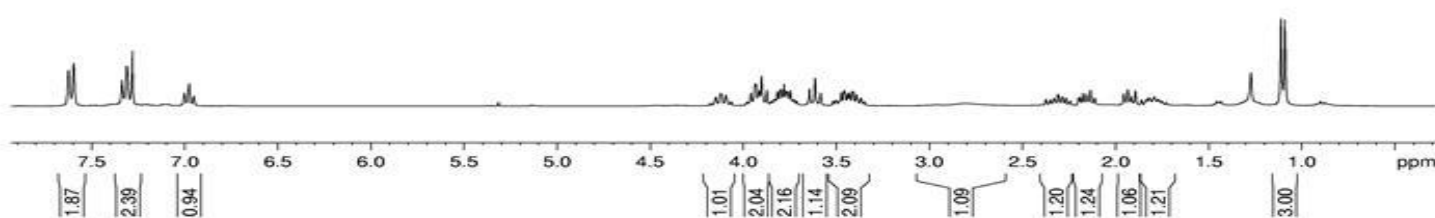
75 MHz, CDCl₃



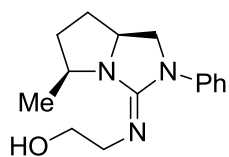


204

300 MHz, CDCl₃

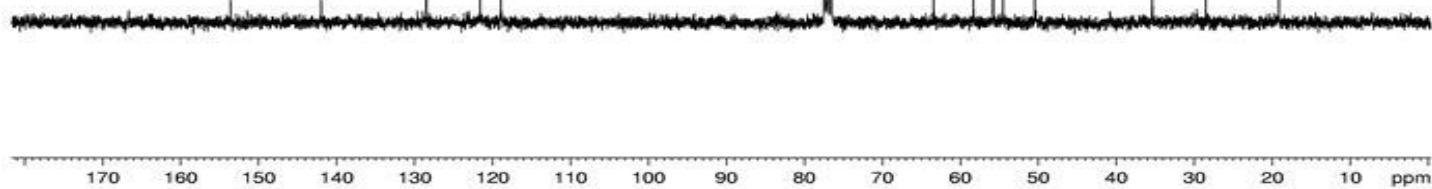


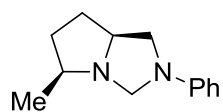
1D carbon with proton decoupling



204

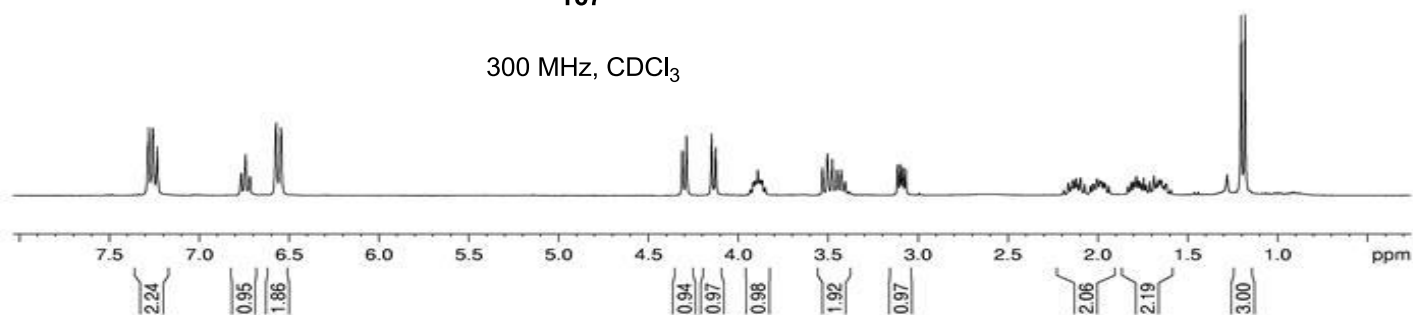
75 MHz, CDCl₃



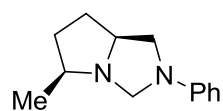


167

300 MHz, CDCl₃

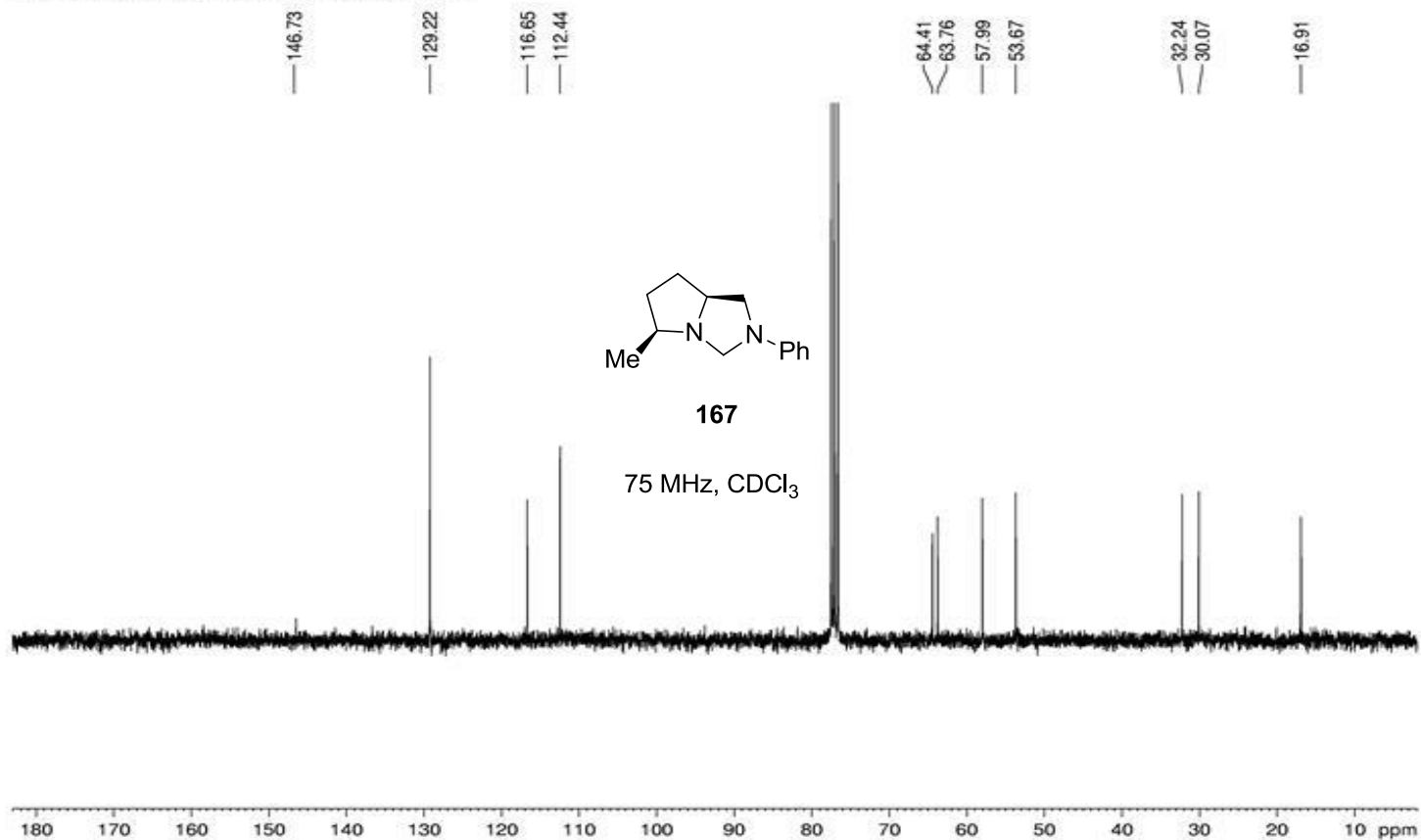


1D carbon with proton decoupling



167

75 MHz, CDCl₃



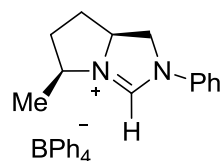
1D proton

9.151

7.683
7.659
7.377
7.358
6.965
6.943
6.919
6.820
6.797

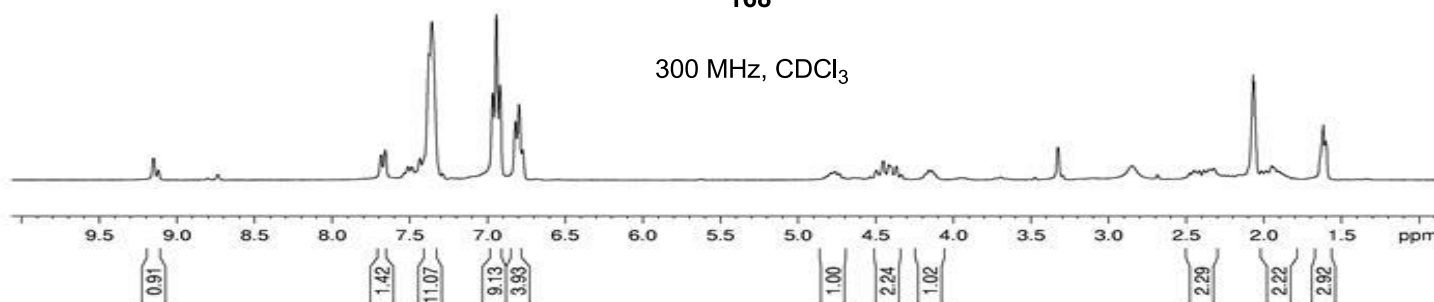
4.767
4.760
4.733
4.493
4.453
4.447
4.416
4.365
4.335
4.157
4.136

2.474
2.446
2.417
2.386
2.348
2.320
2.012
1.984
1.947
1.939
1.908
1.899
1.880
1.616
1.601



168

300 MHz, CDCl₃



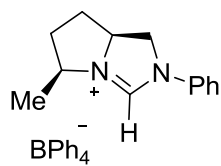
1D carbon with proton decoupling

165.02
164.36
163.71
163.06
152.00
136.11
132.67
129.79
125.16
125.13
121.40
119.88

64.62
64.46
54.87
54.22

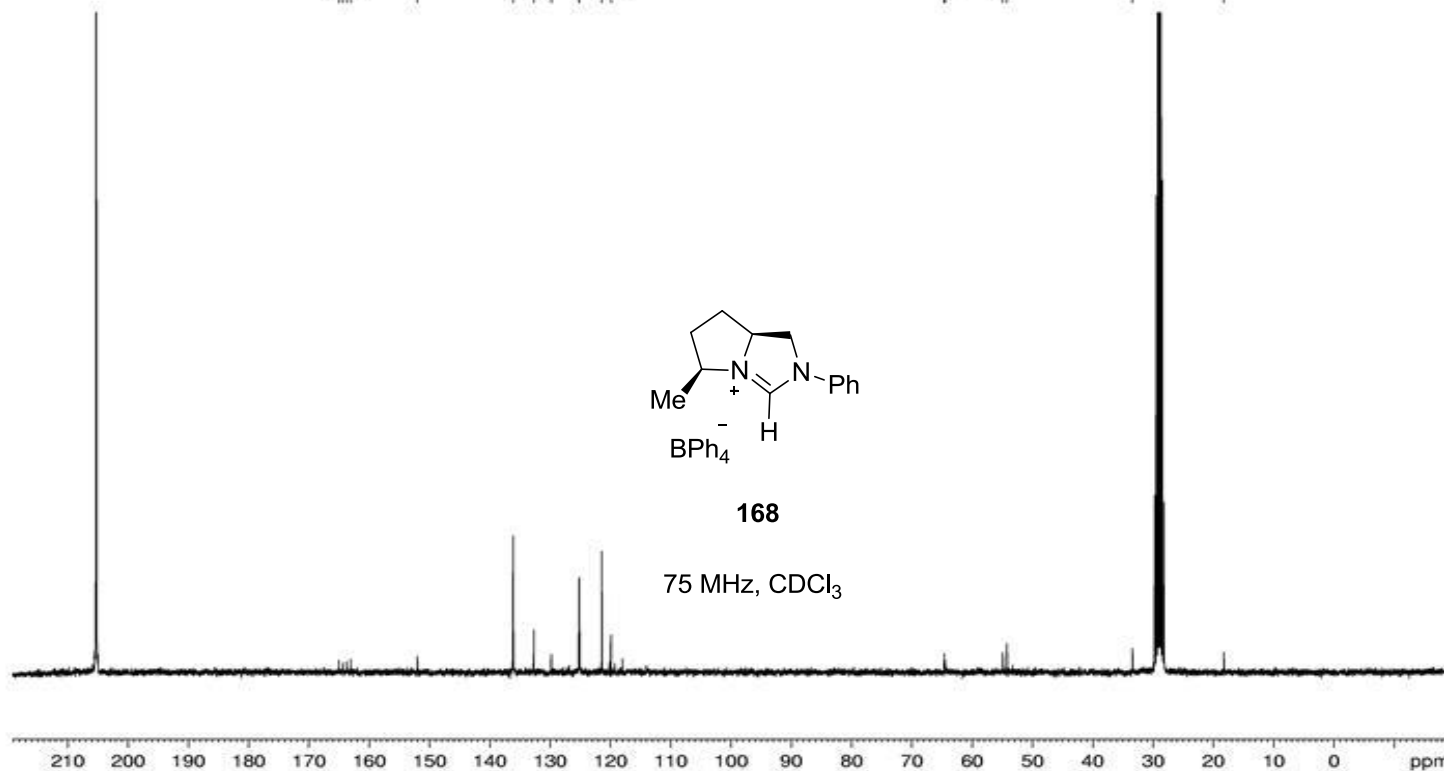
33.38

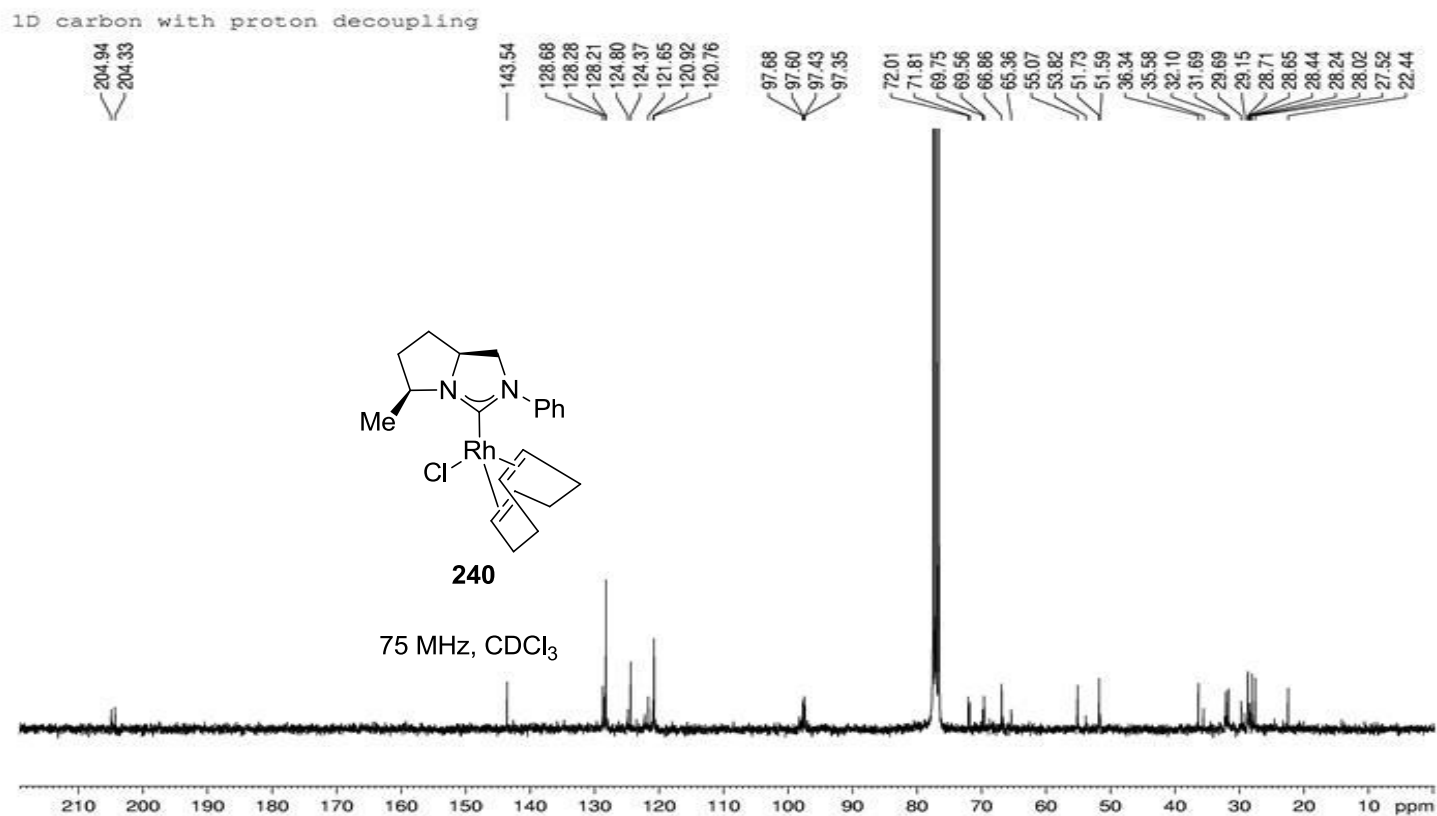
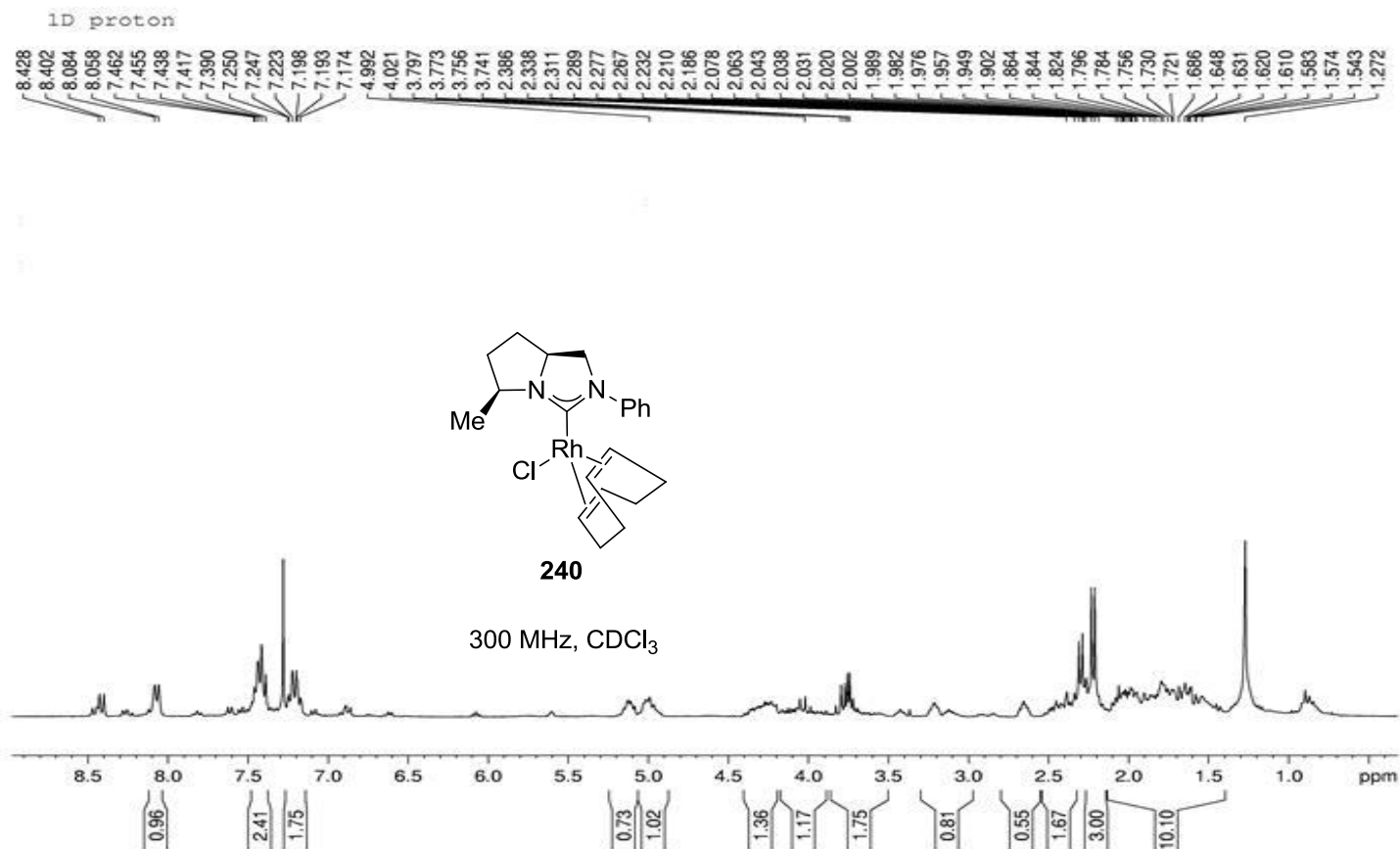
18.23

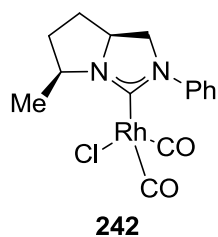


168

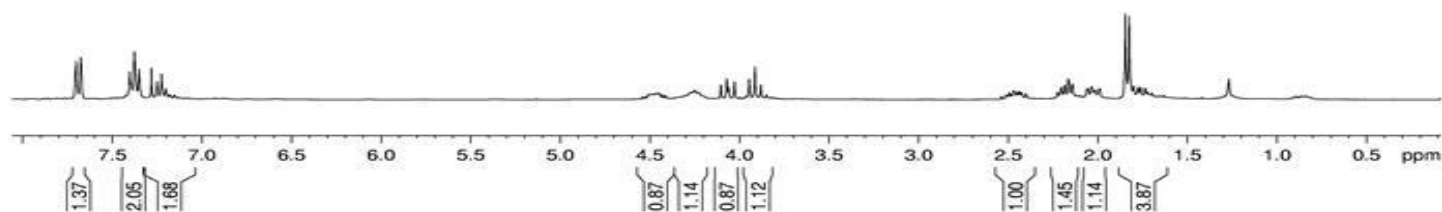
75 MHz, CDCl₃



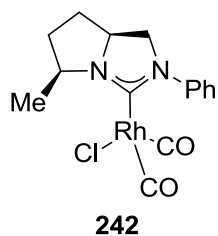




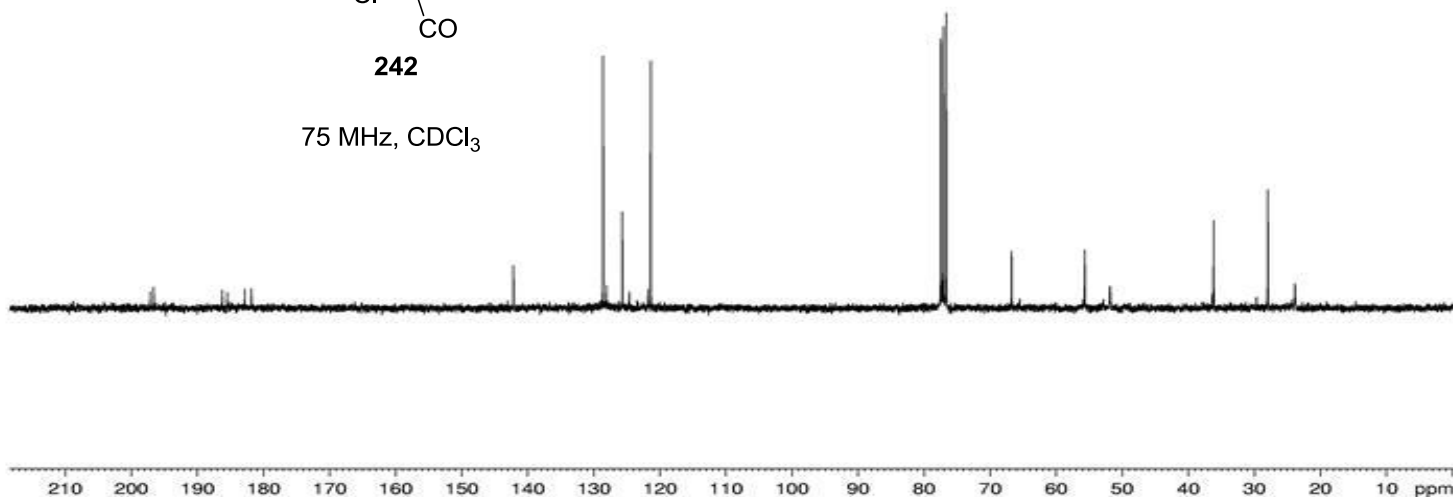
150 MHz, CDCl₃

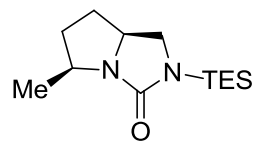


1D carbon with proton decoupling



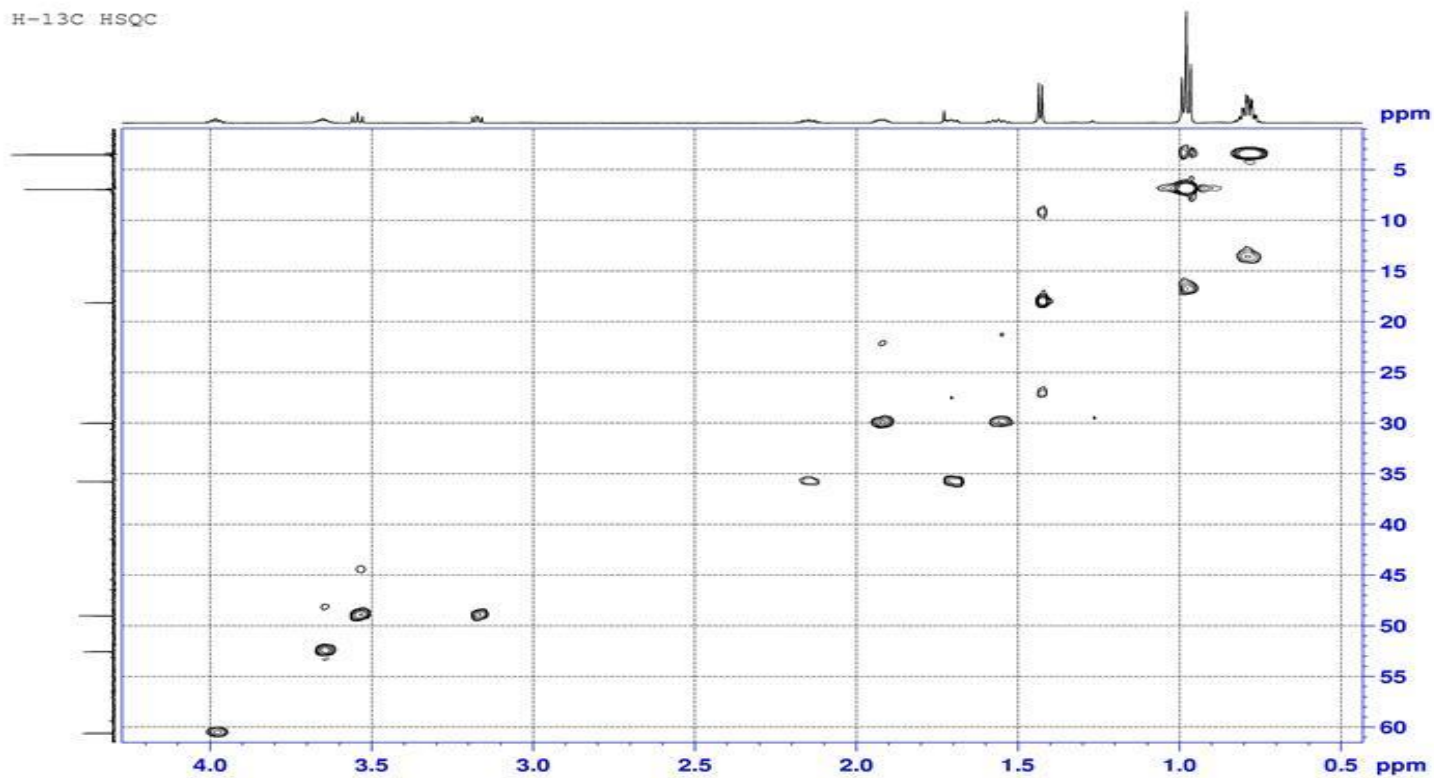
75 MHz, CDCl₃



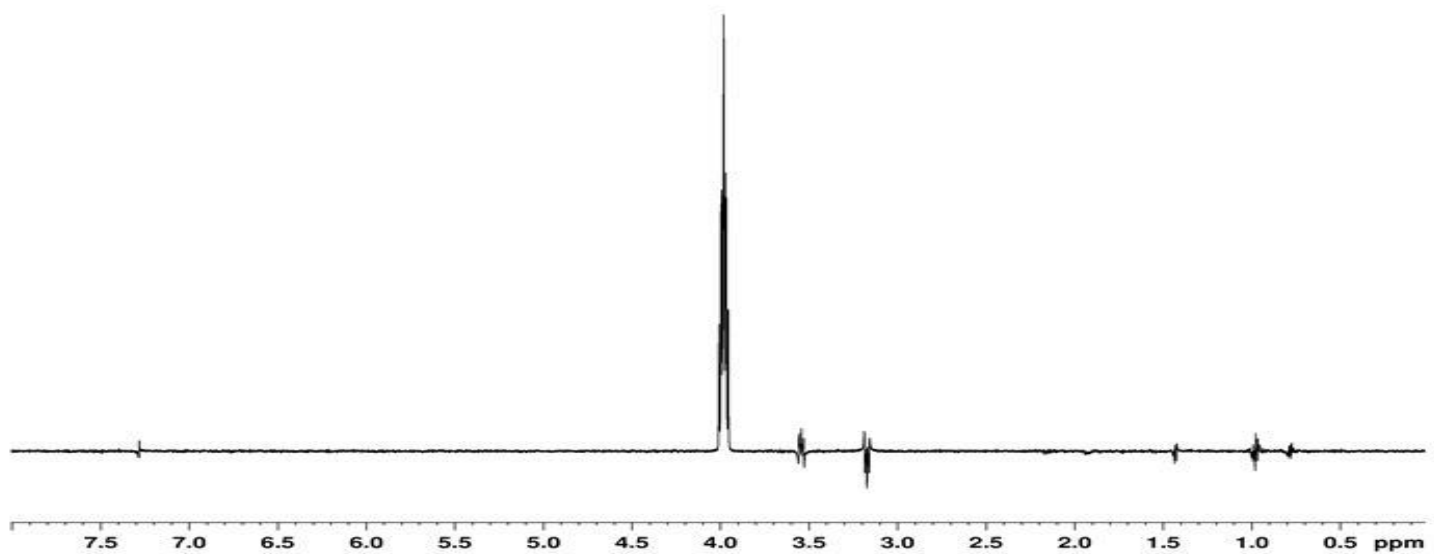


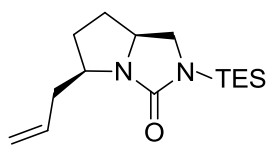
181

H-13C HSQC

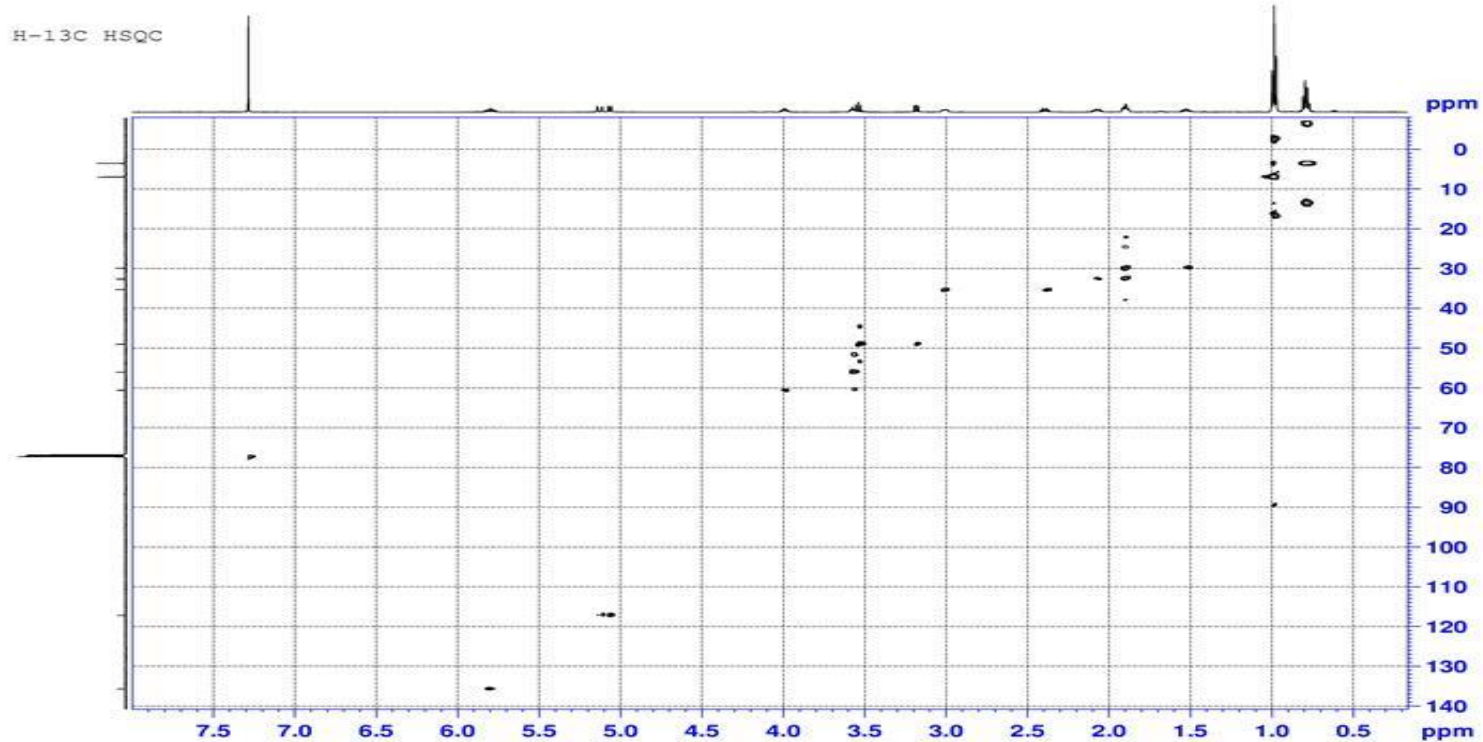
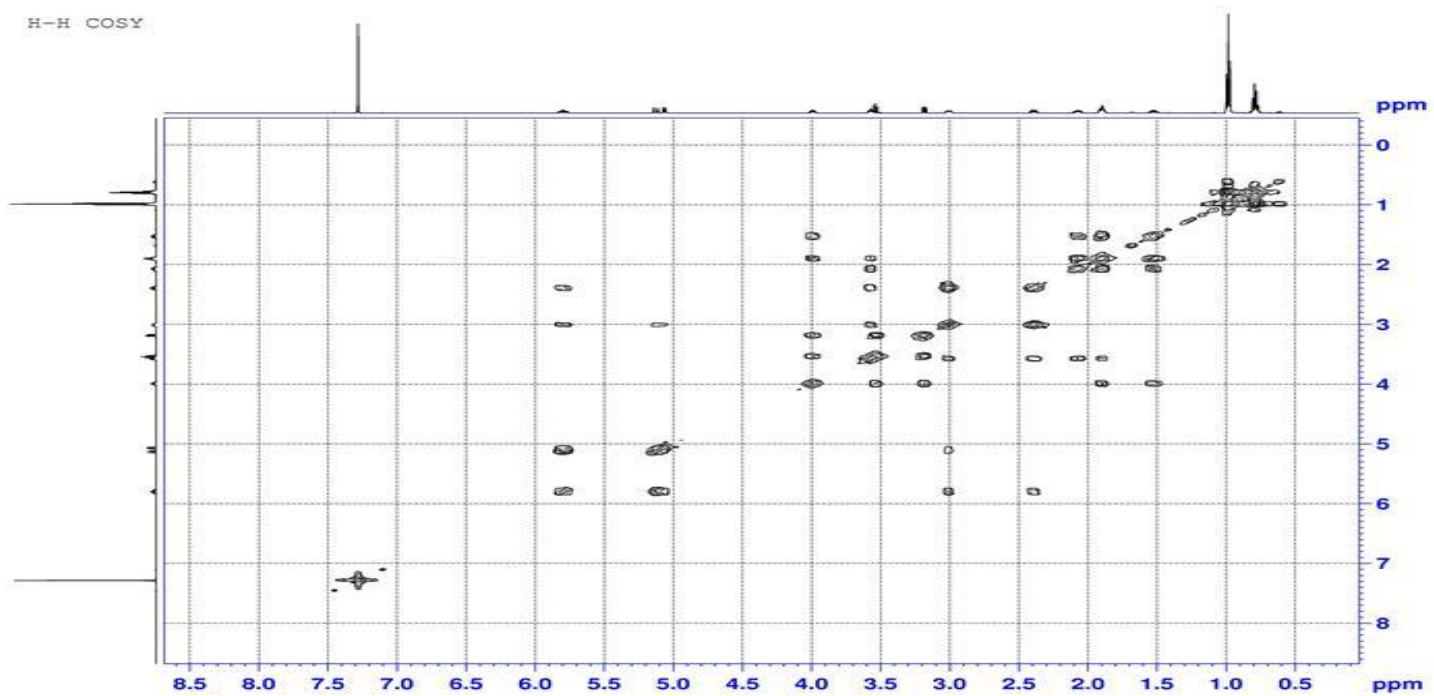


SENOGP

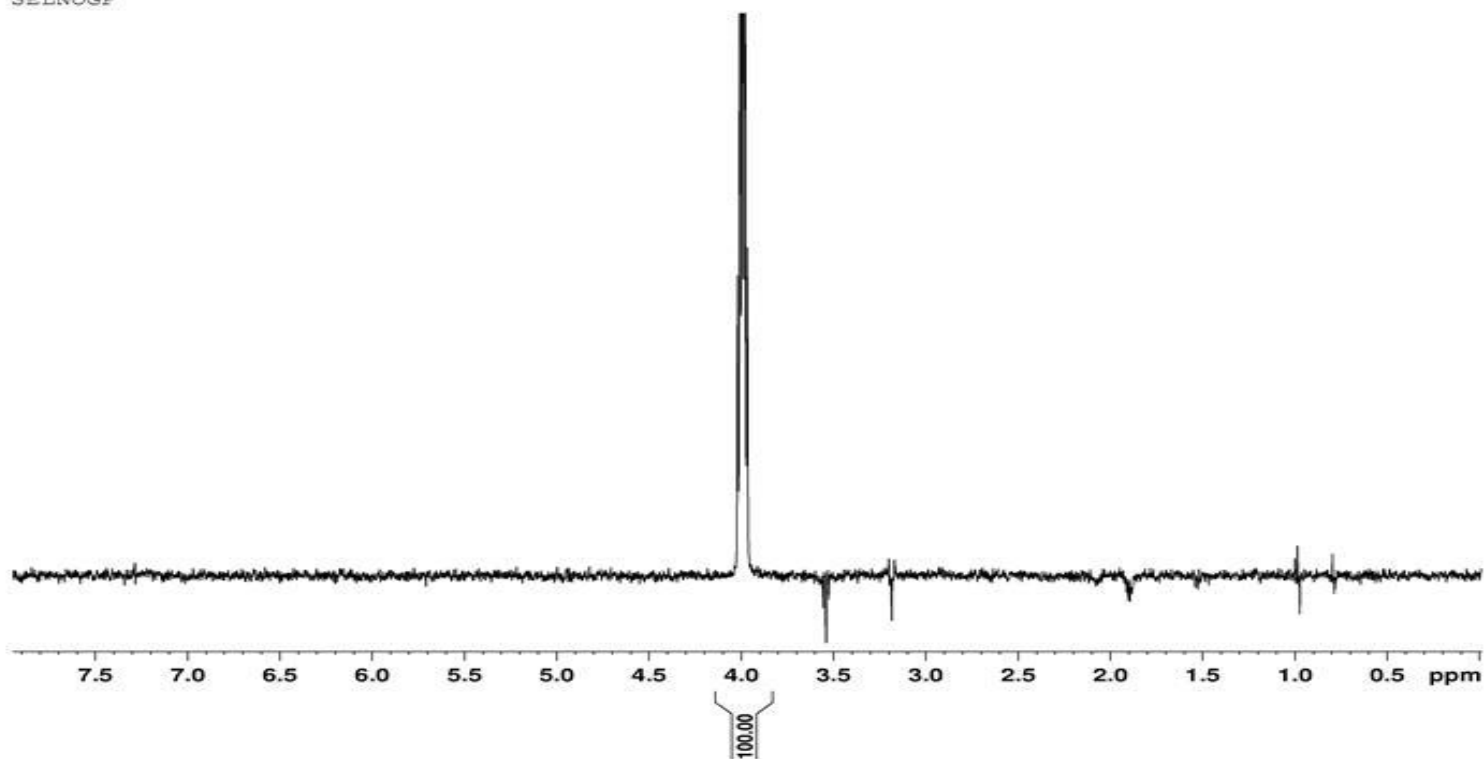




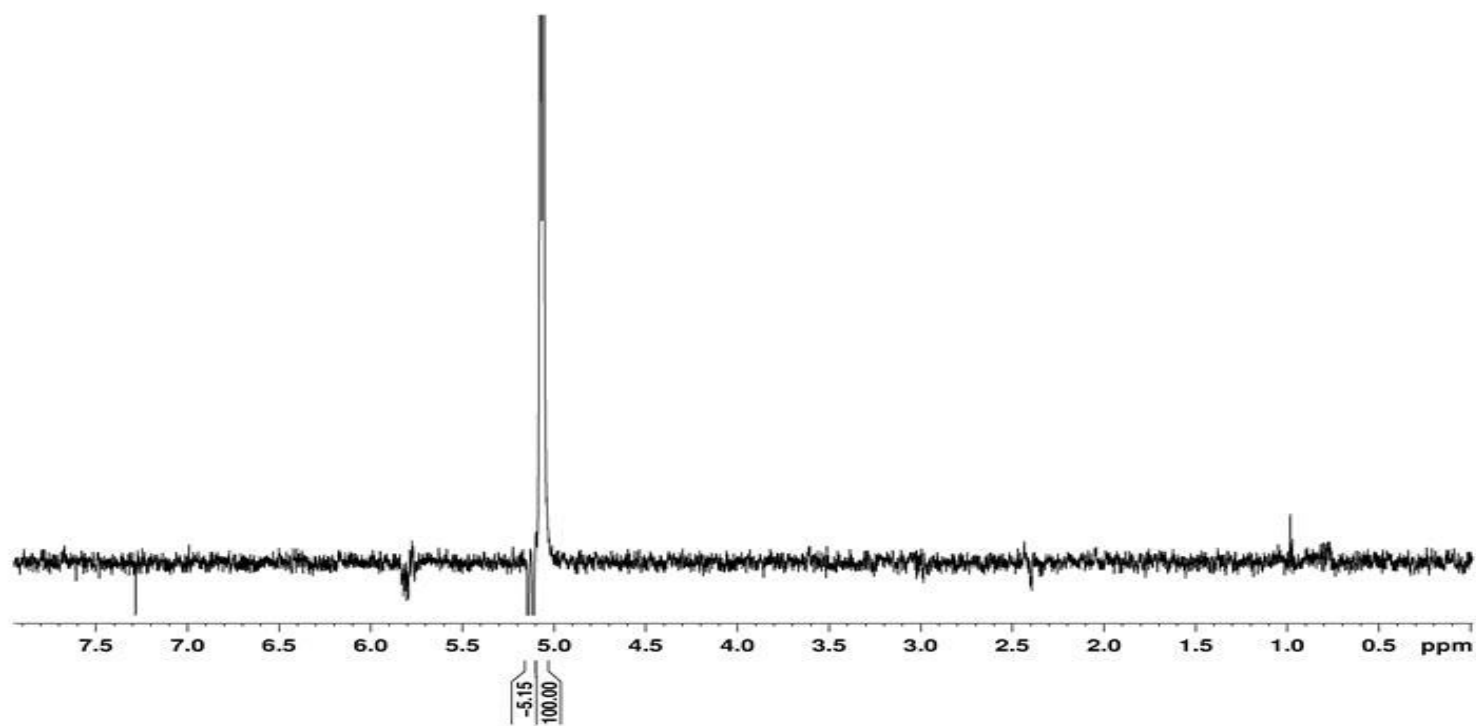
183

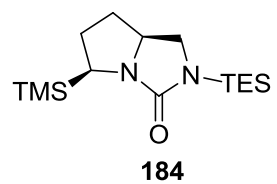


SENOGP

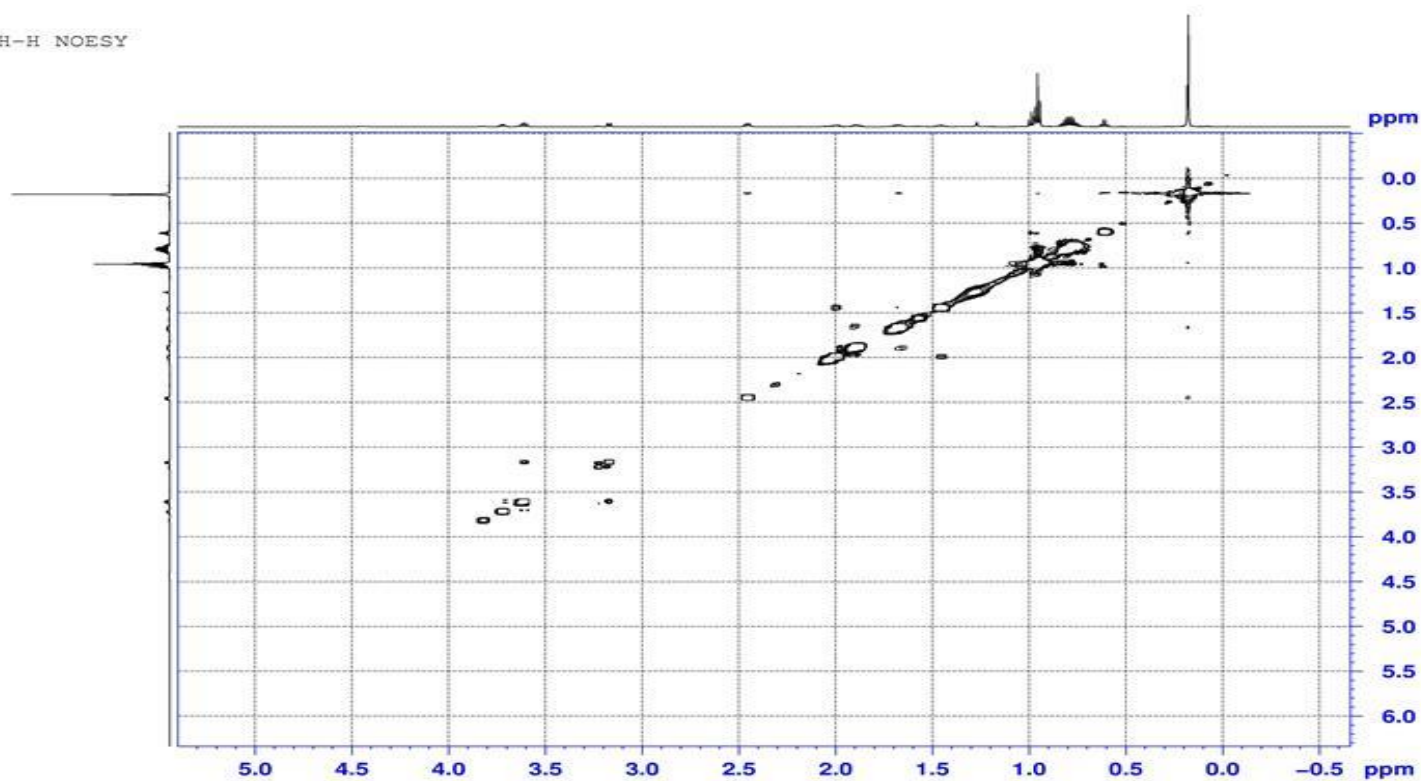


SENOGP

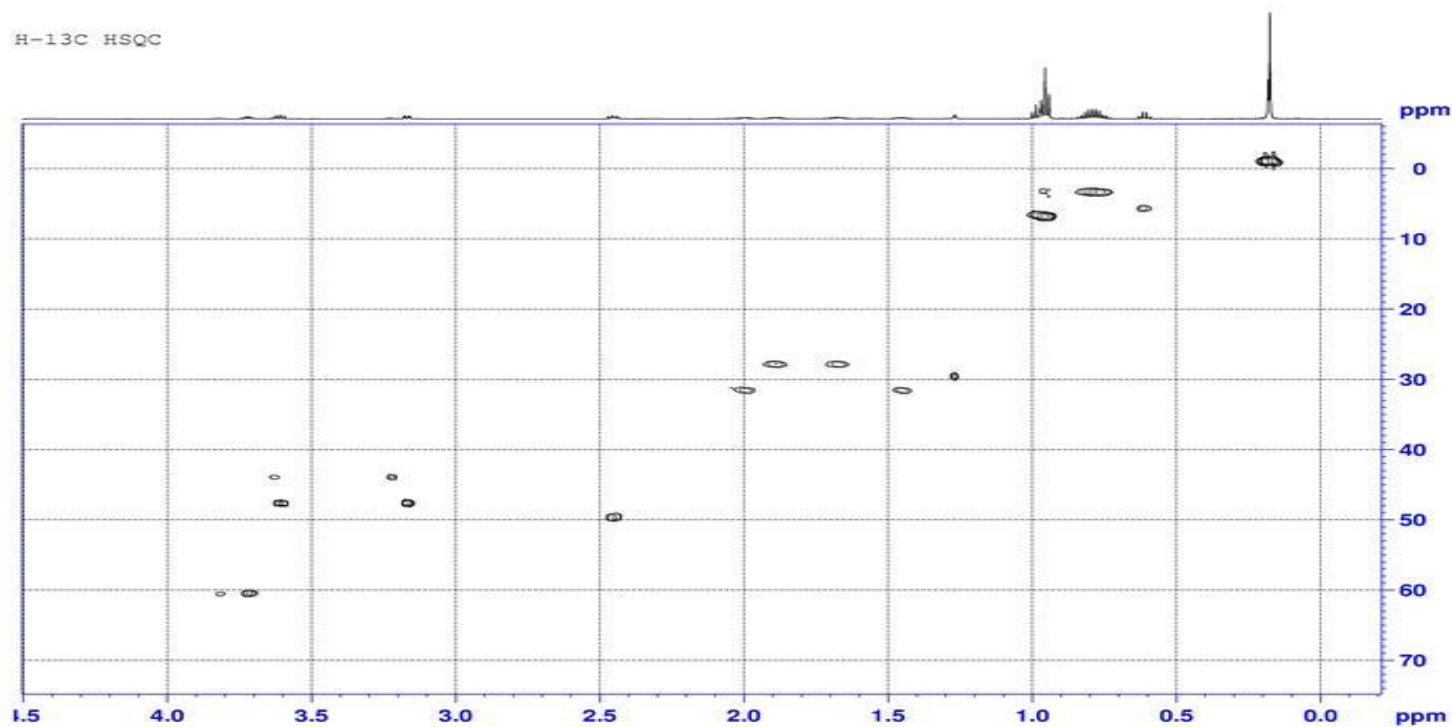


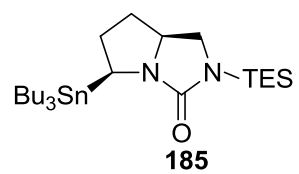


H-H NOESY

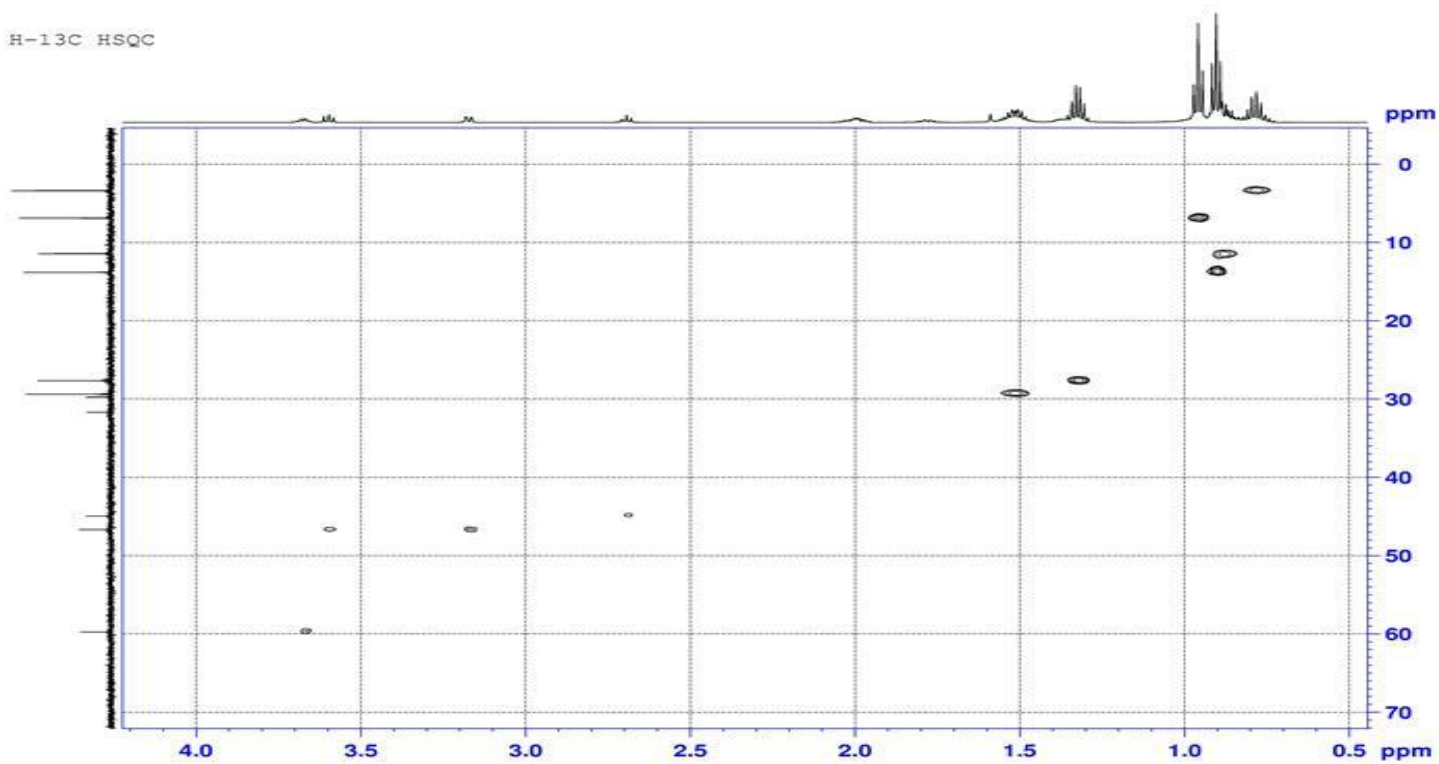


H-13C HSQC

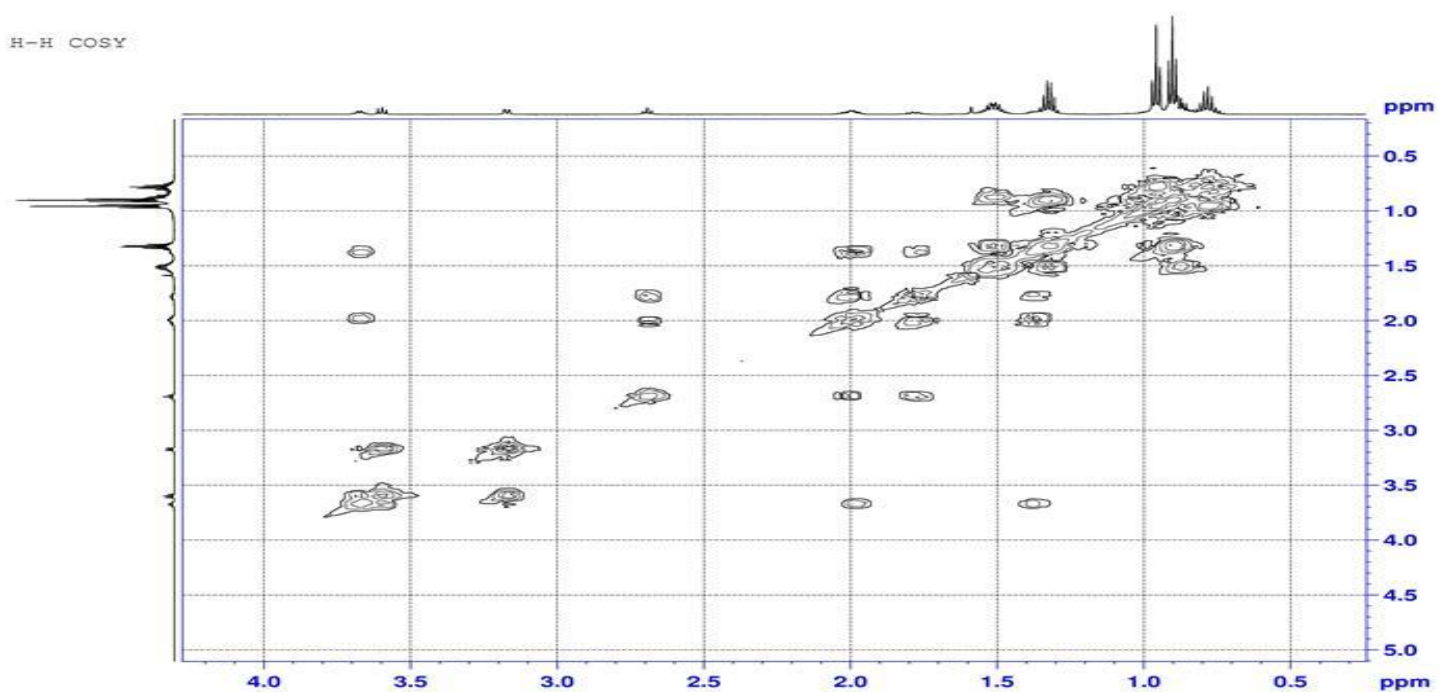




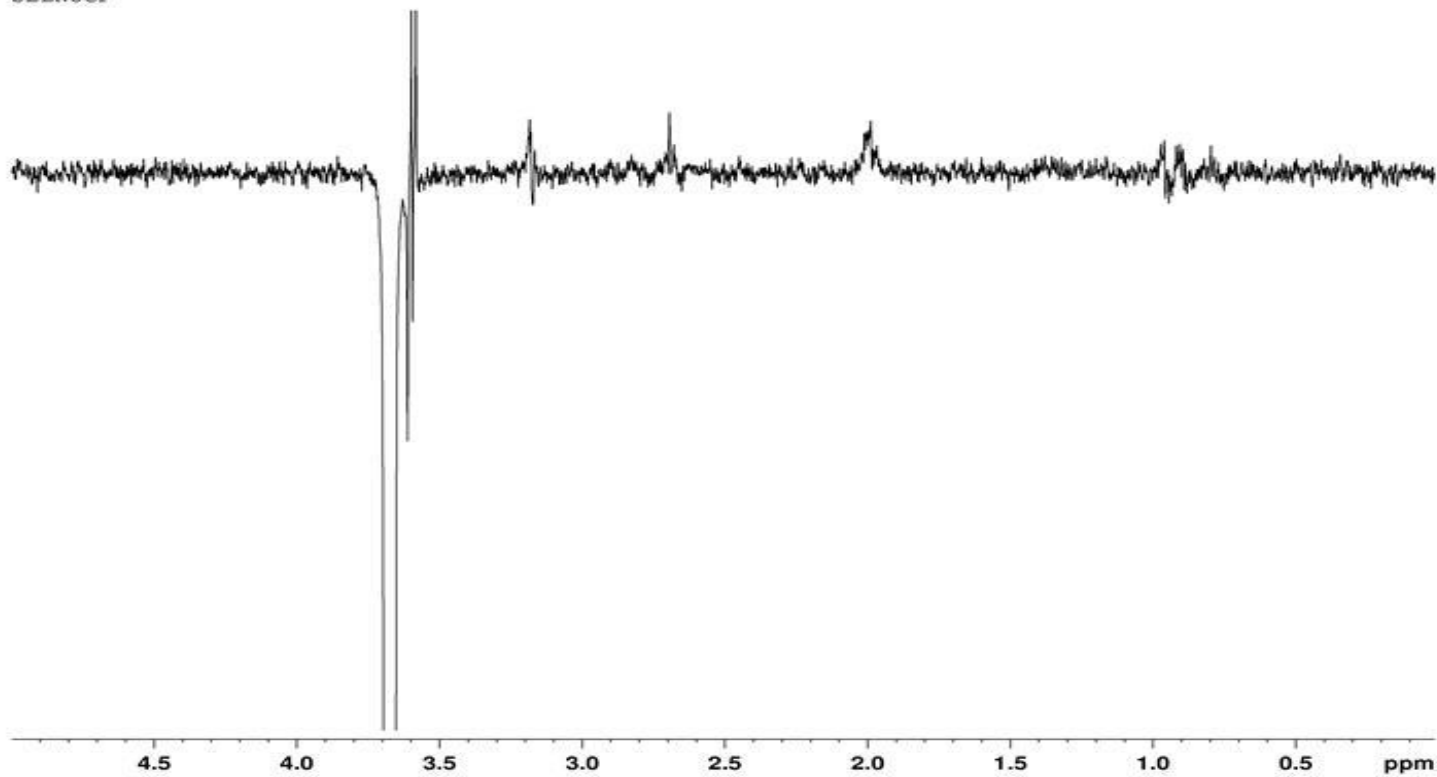
H-13C HSQC



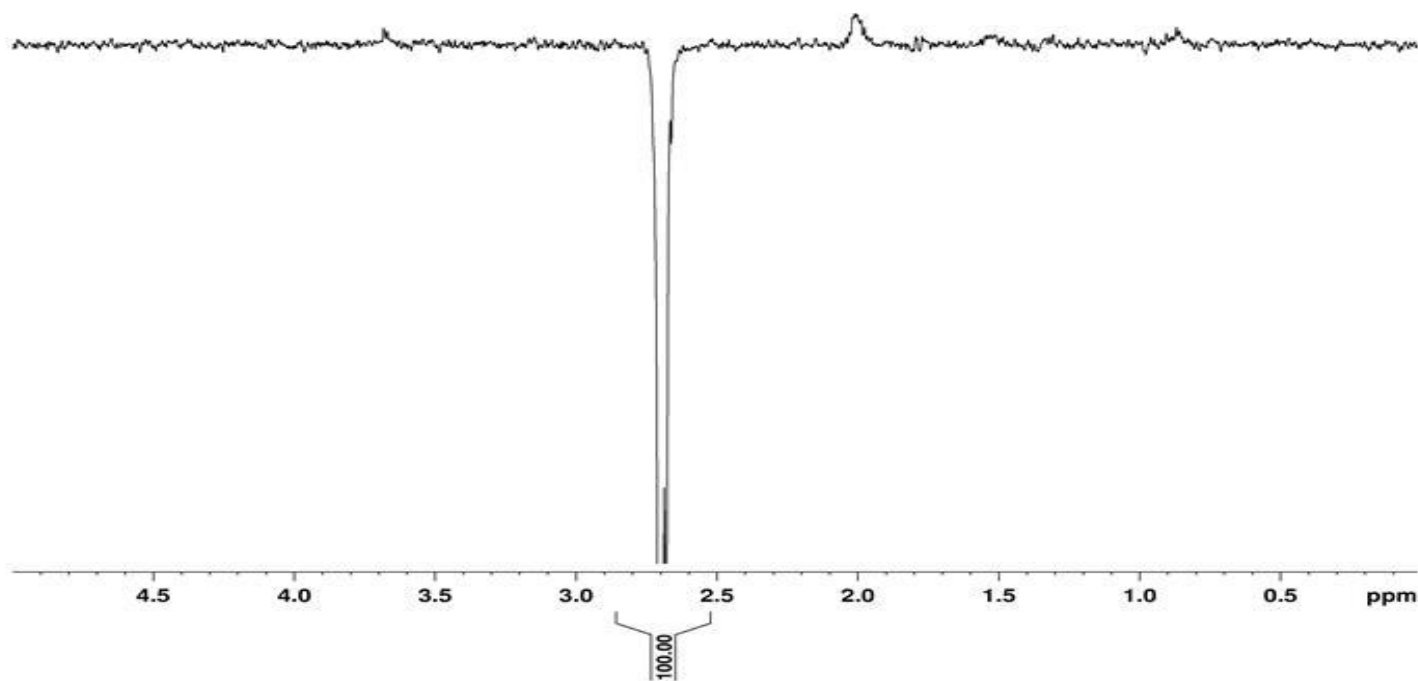
H-H COSY



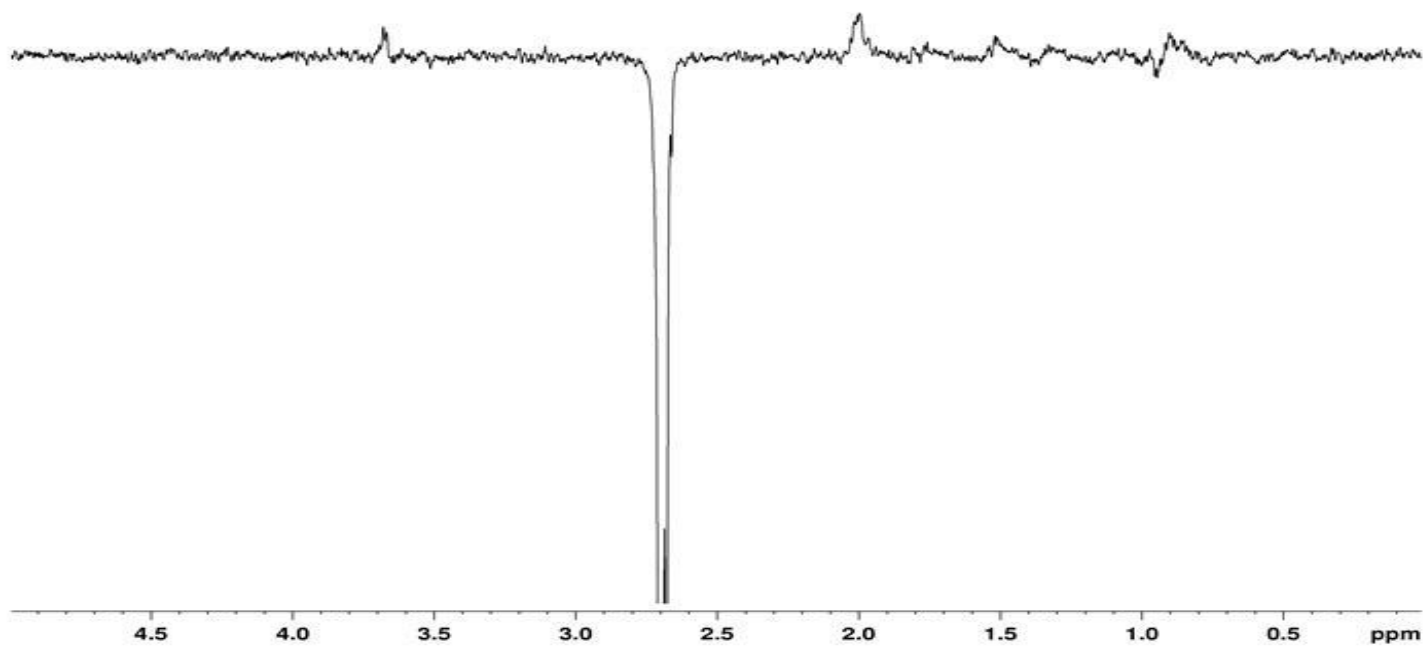
SELNOGP



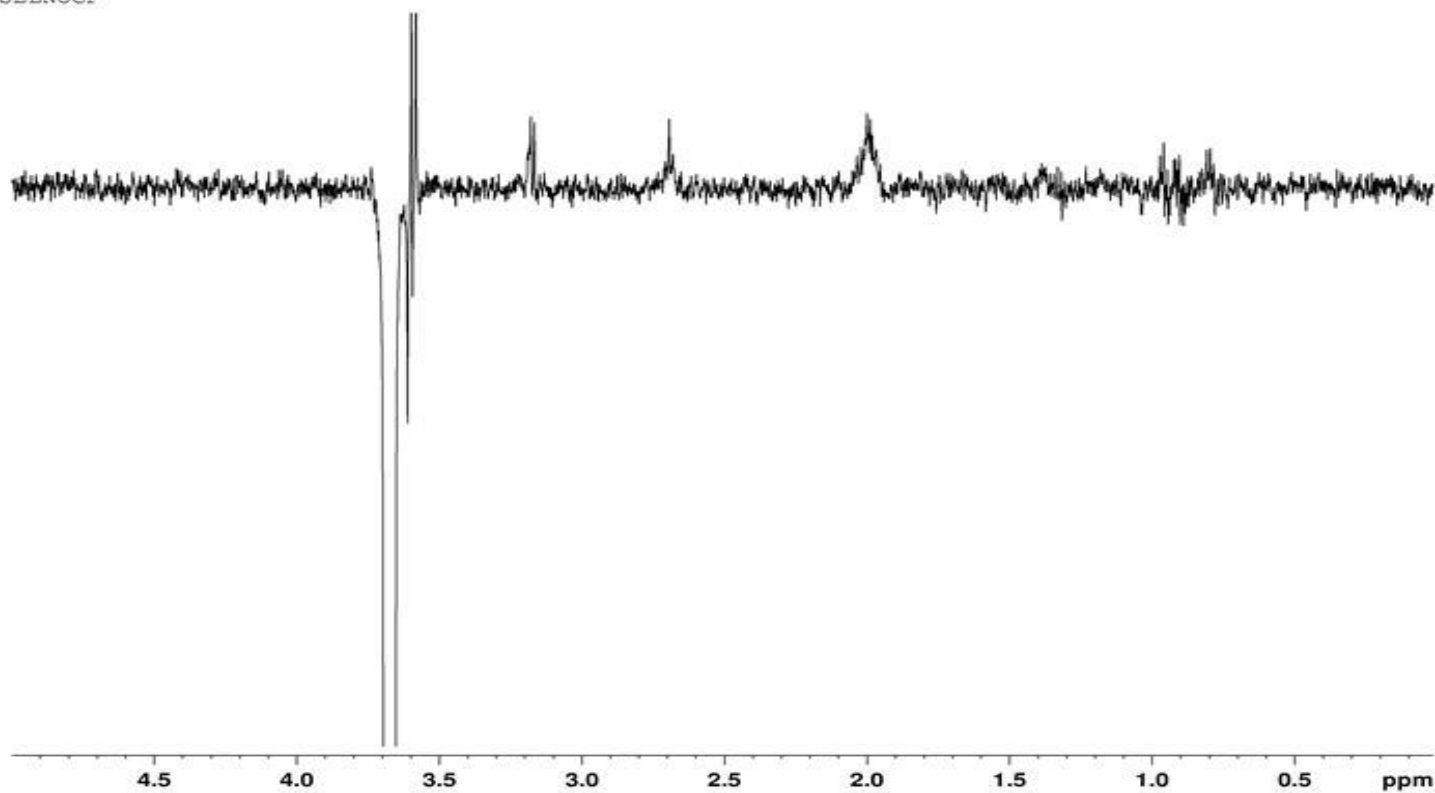
SELNOGP

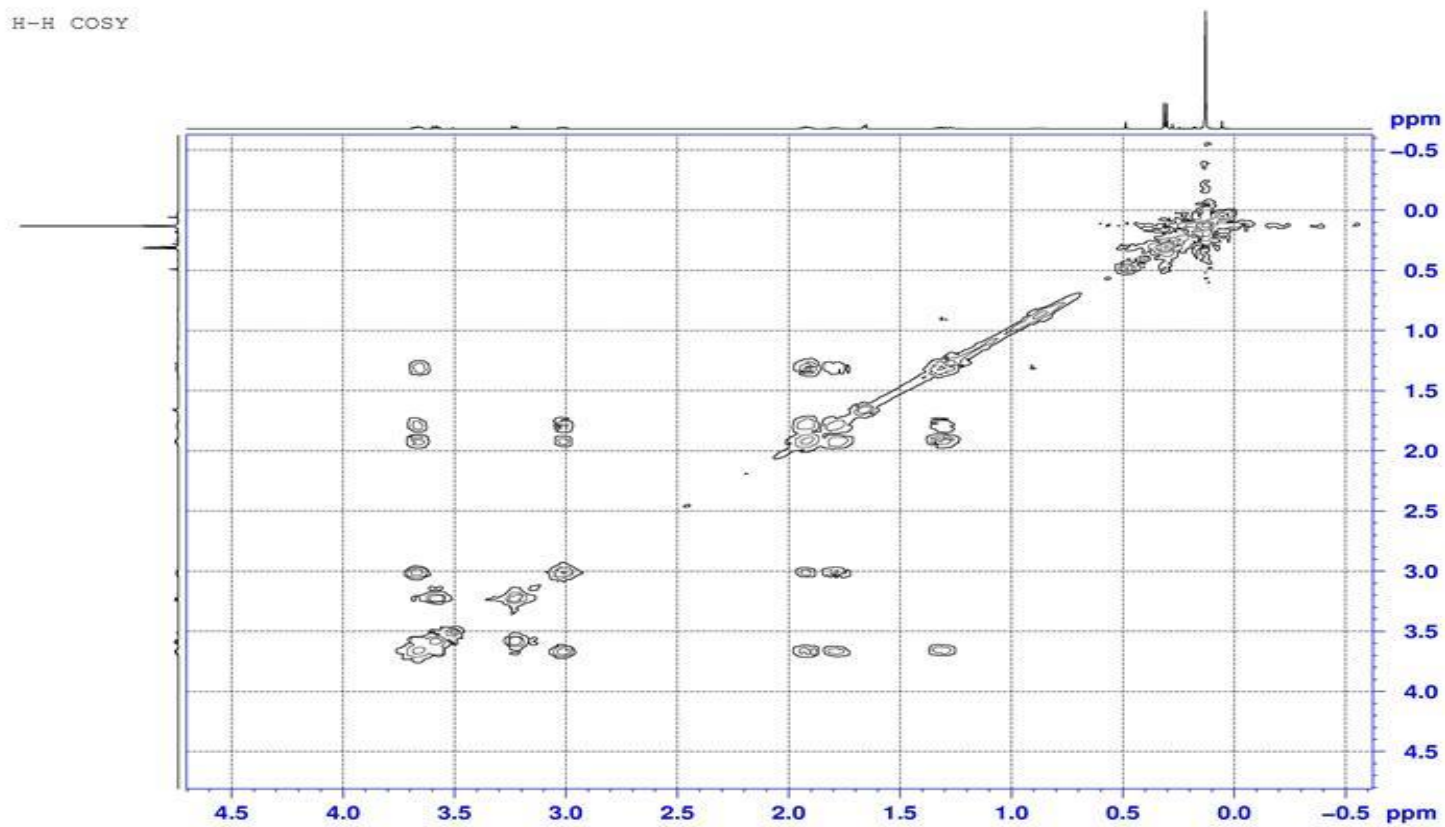
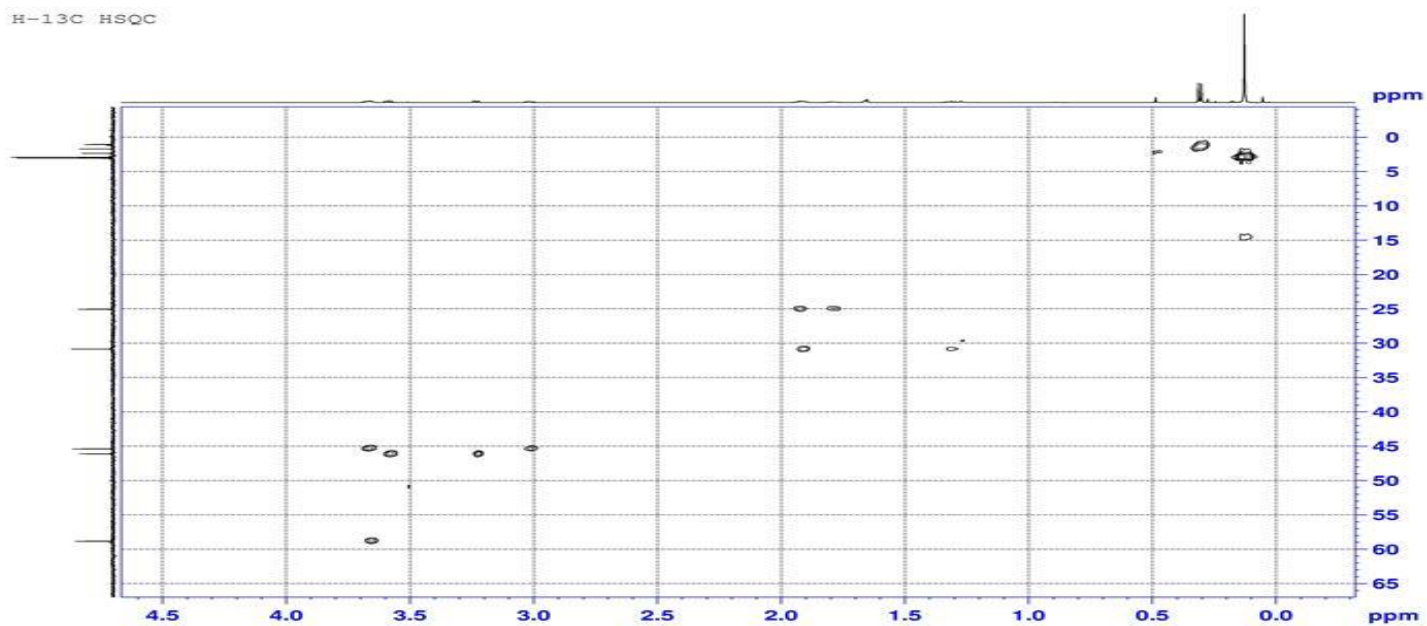


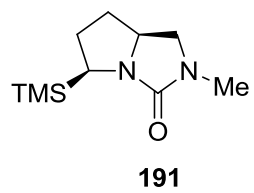
SELNOGP



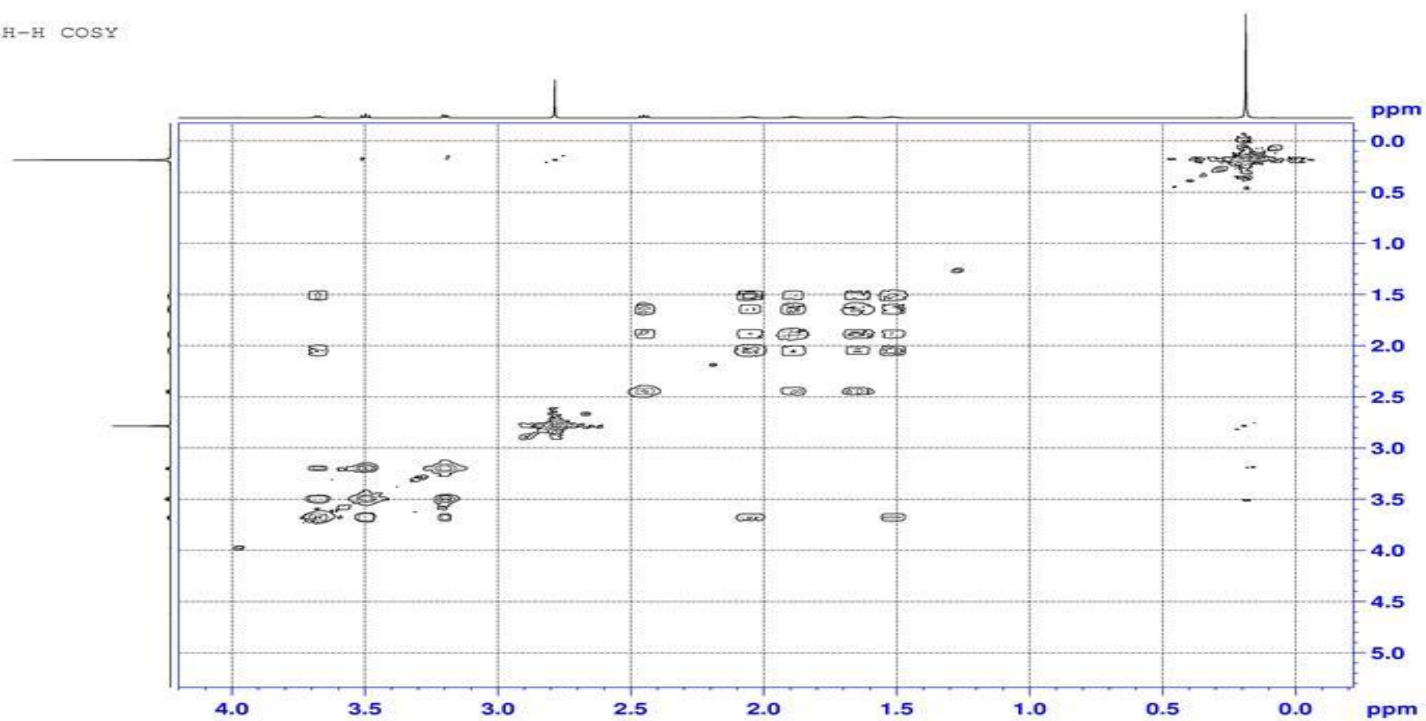
SELNOGP



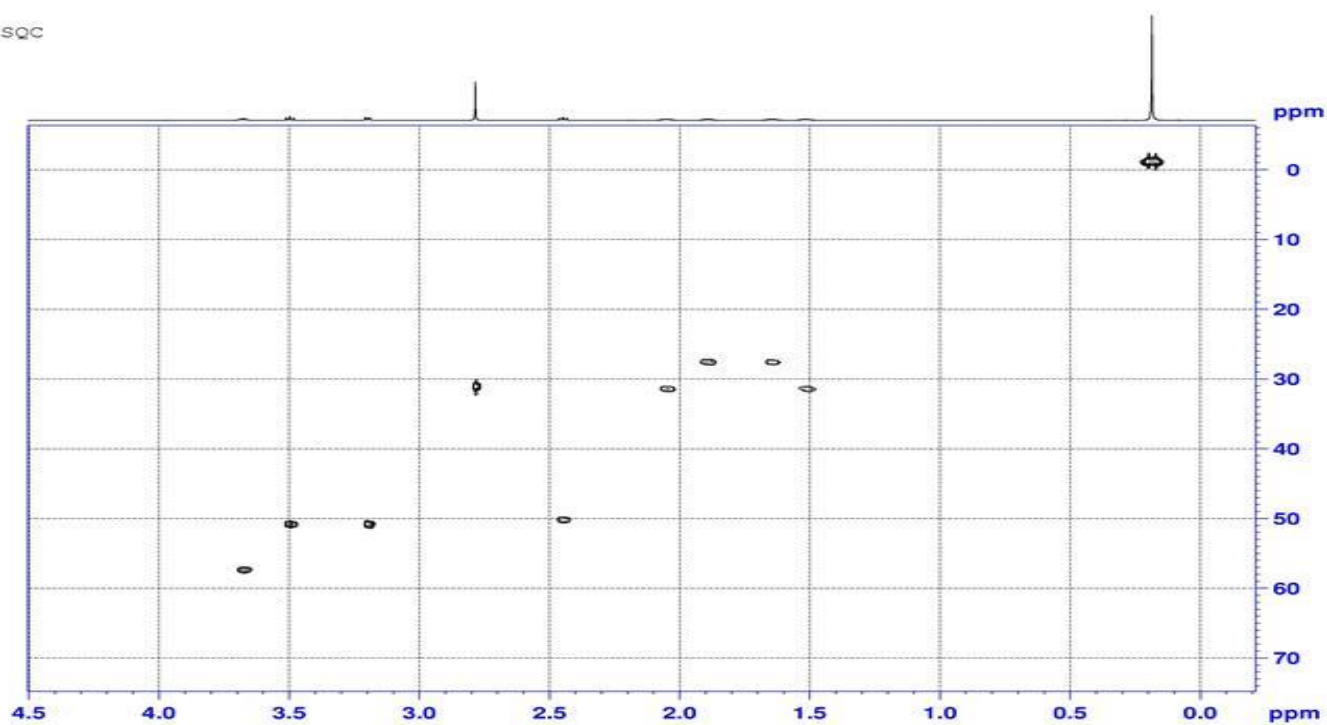


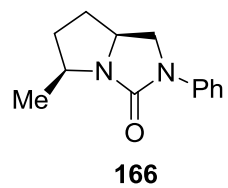


H-H COSY

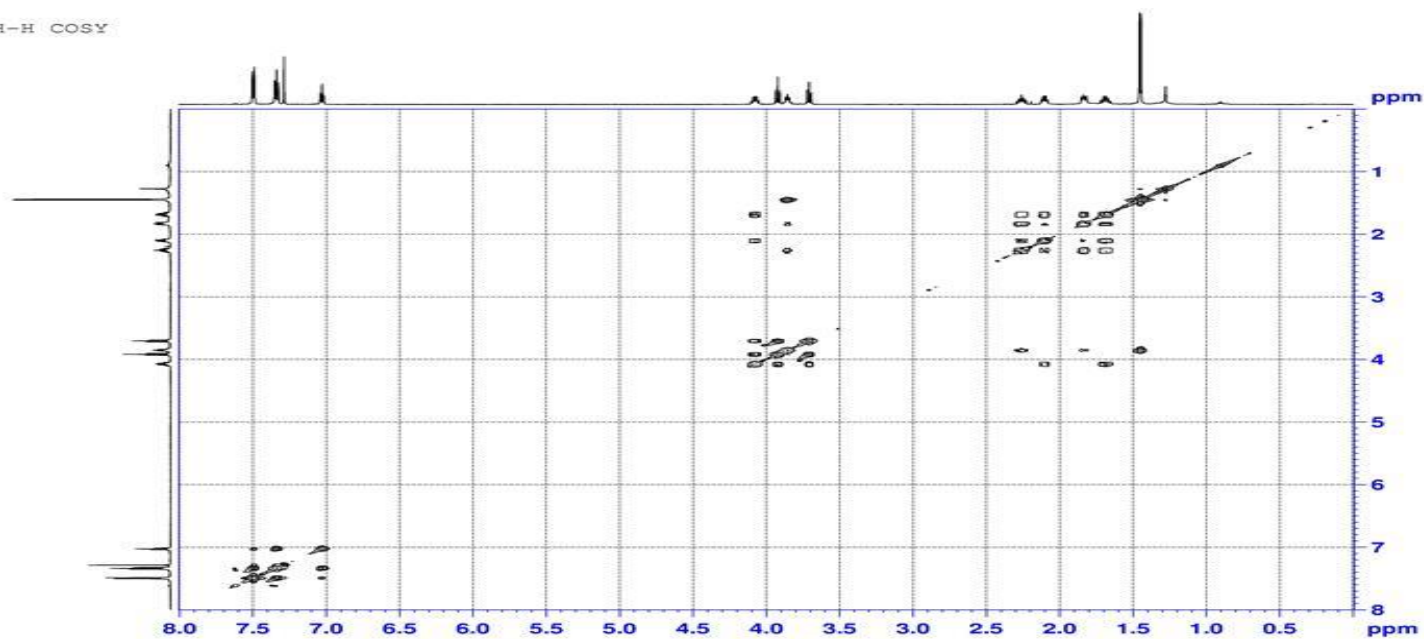


H-13C HSQC

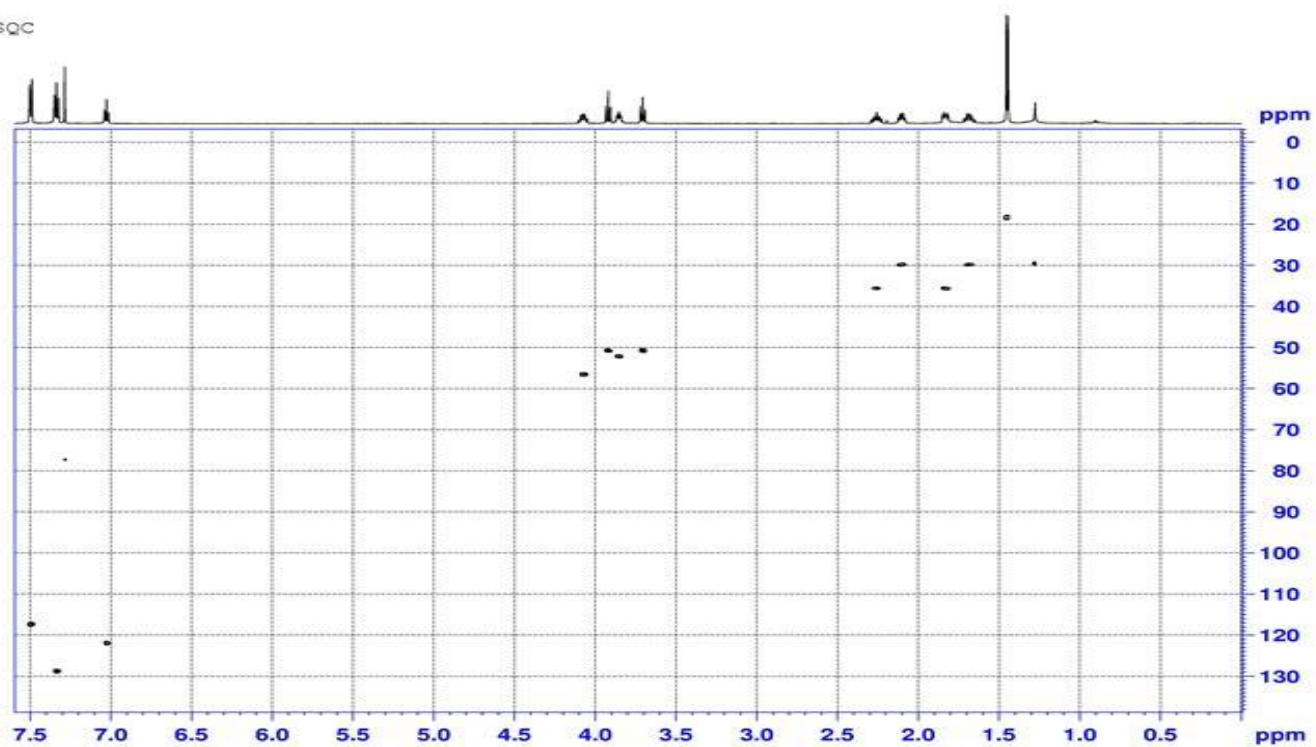


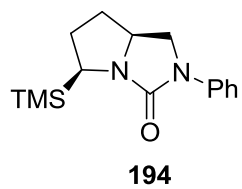


H-H COSY

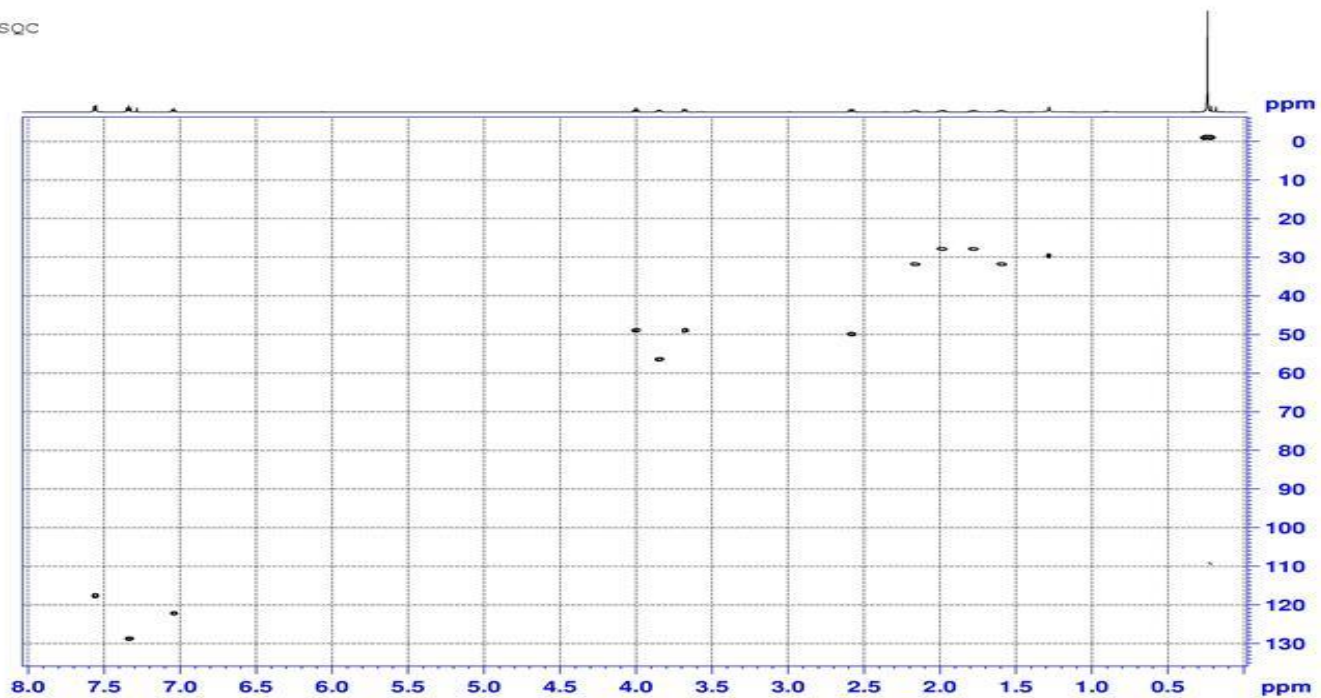


H-13C HSQC

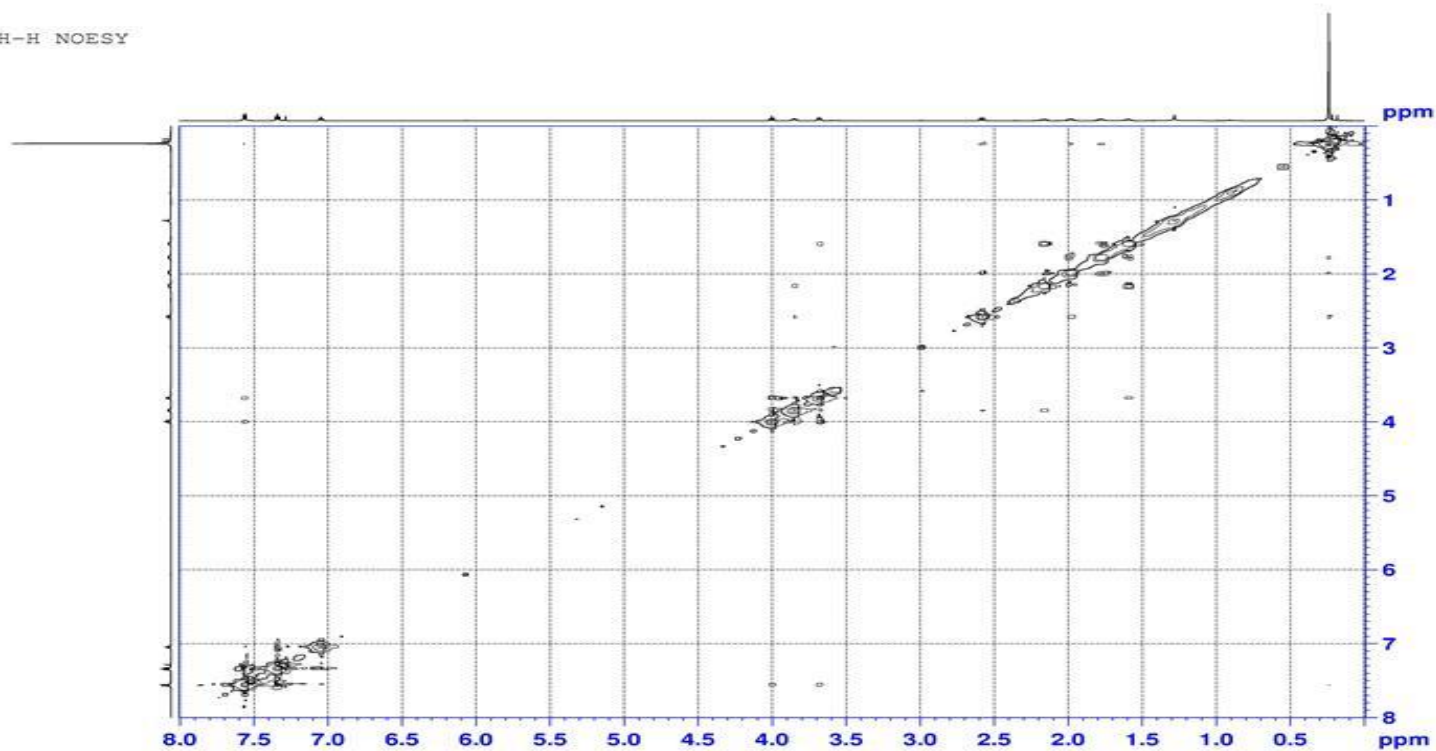


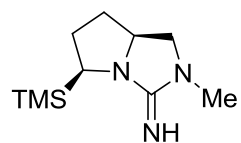


H-13C HSQC



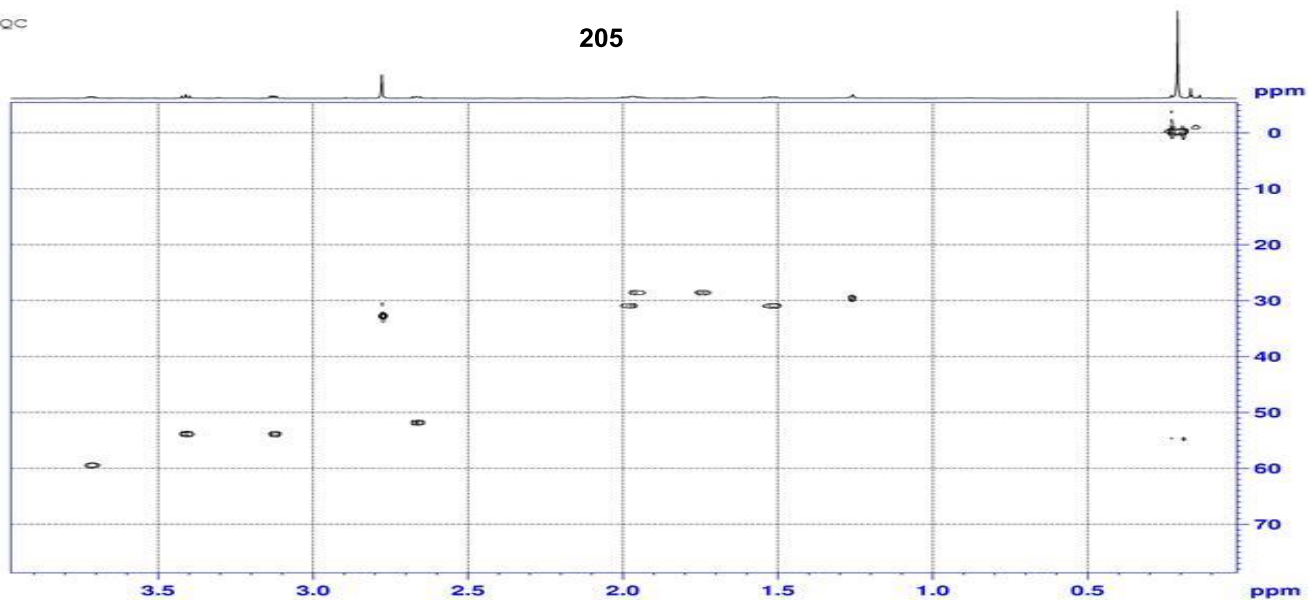
H-H NOESY



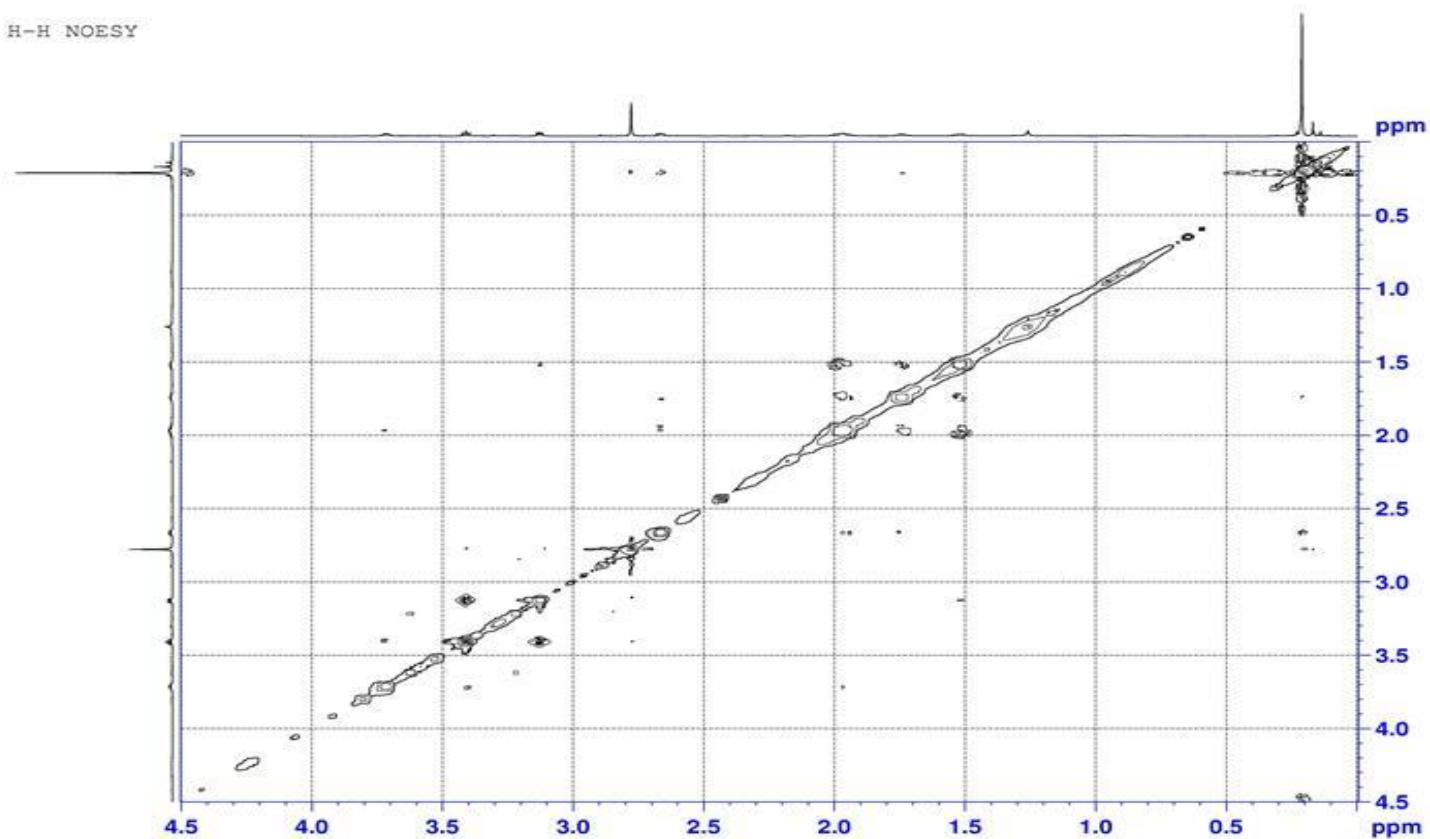


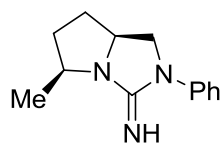
205

H-13C HSQC

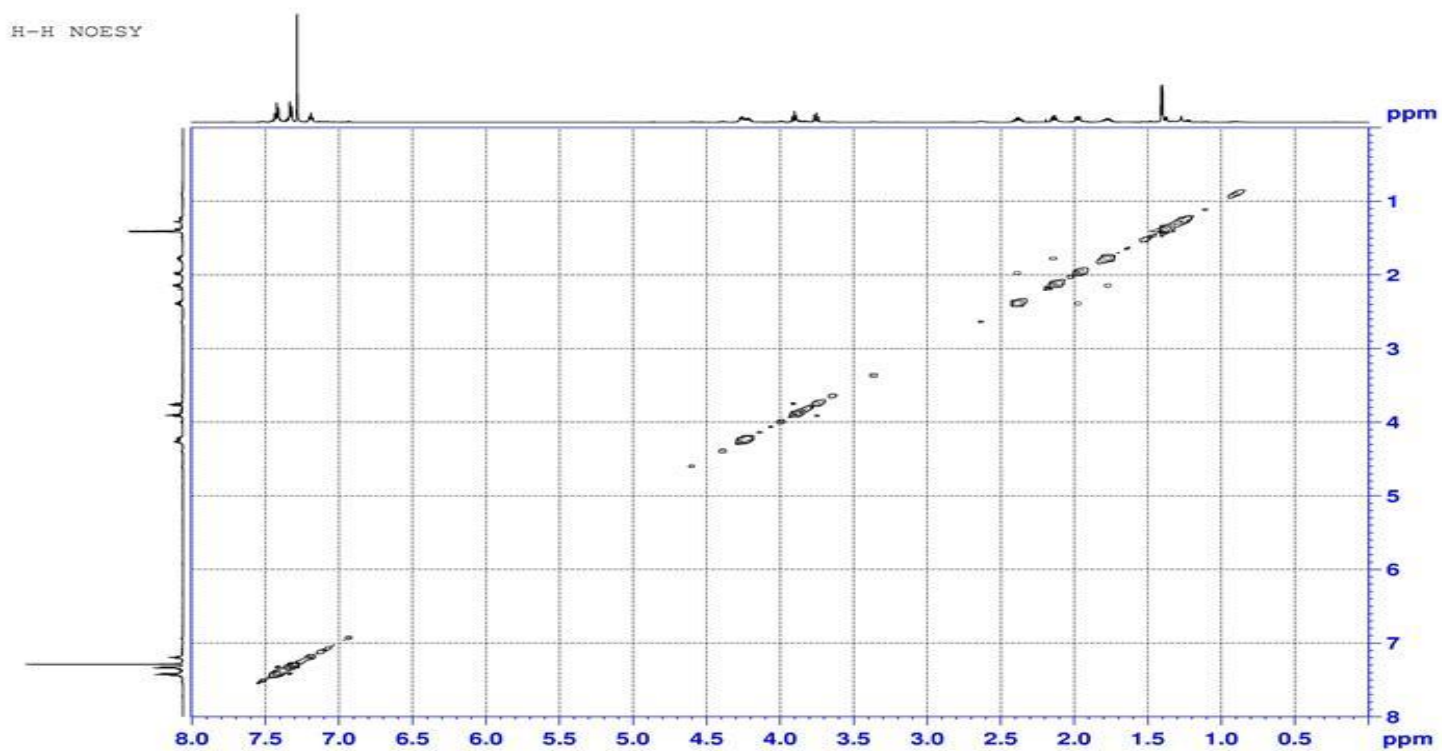
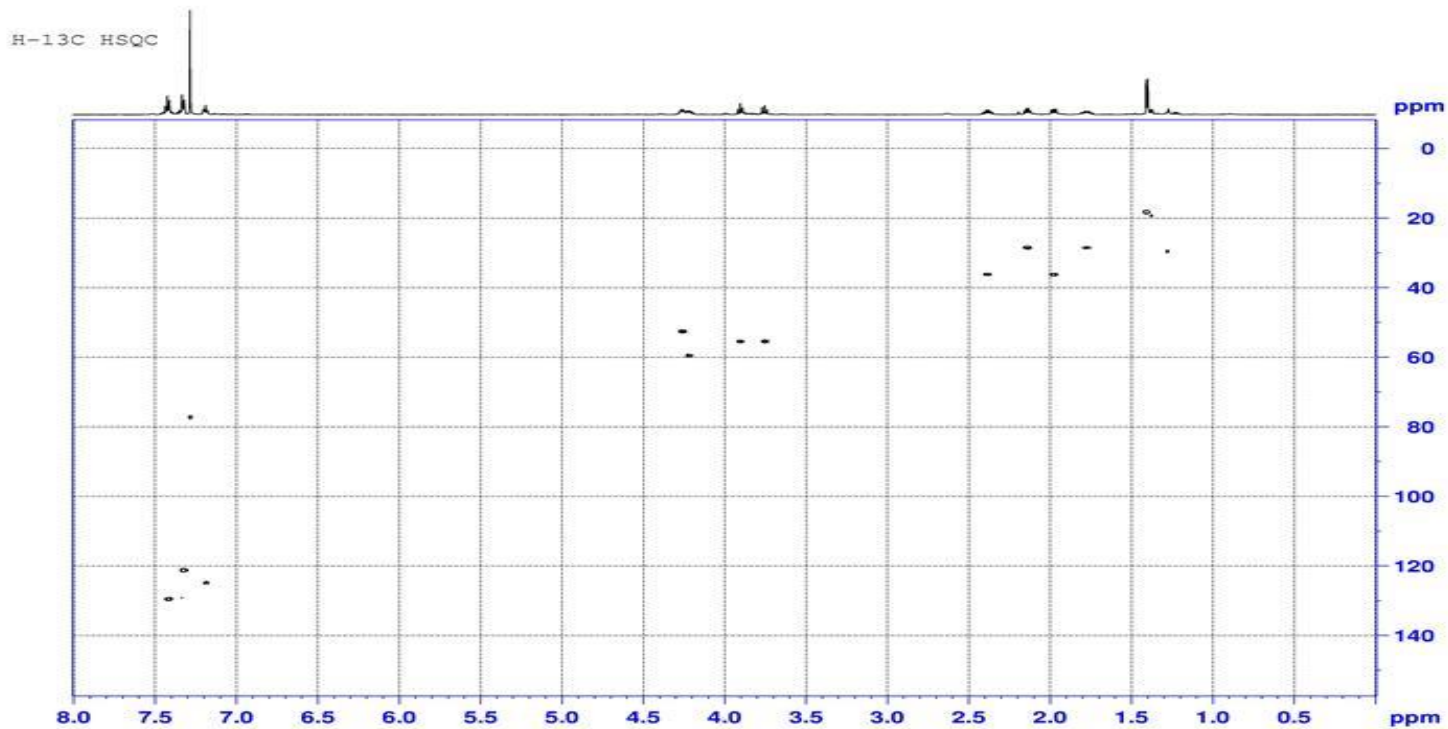


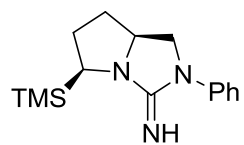
H-H NOESY





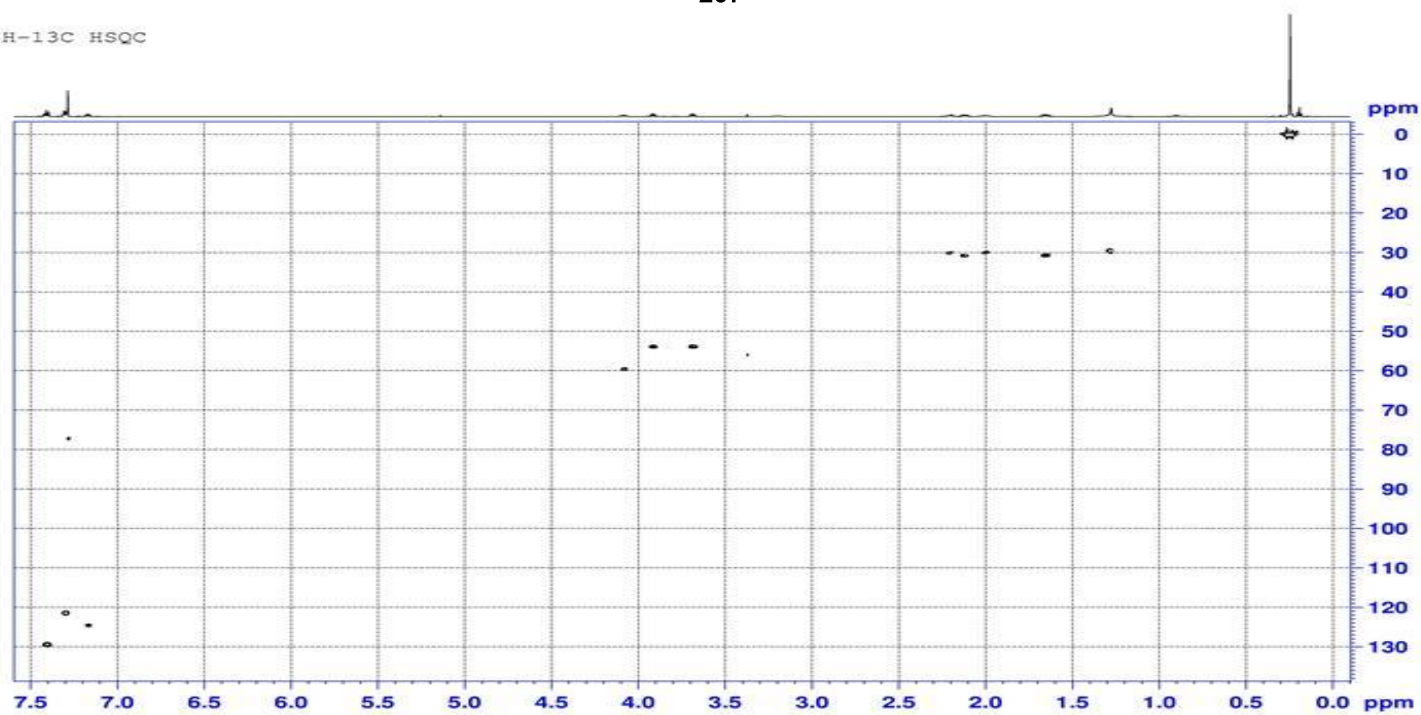
206



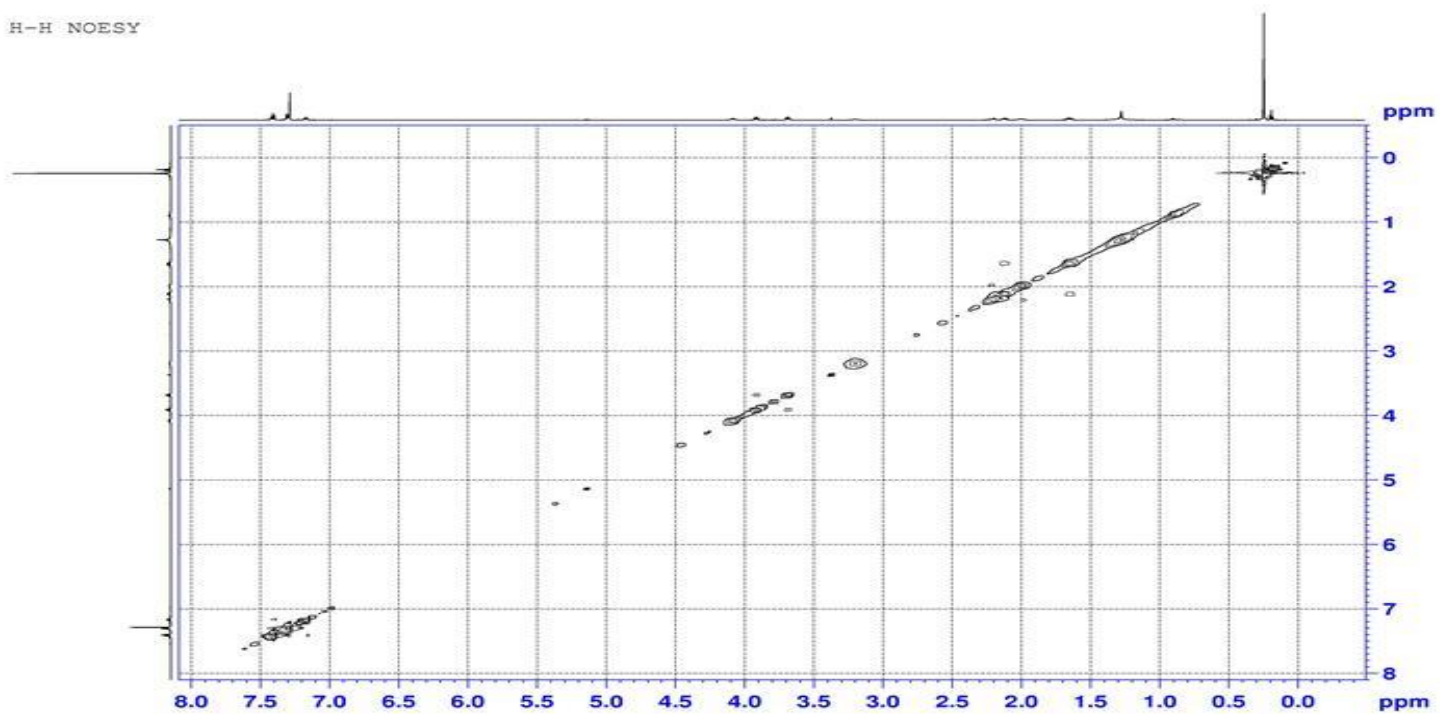


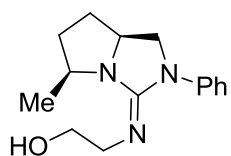
207

H-13C HSQC



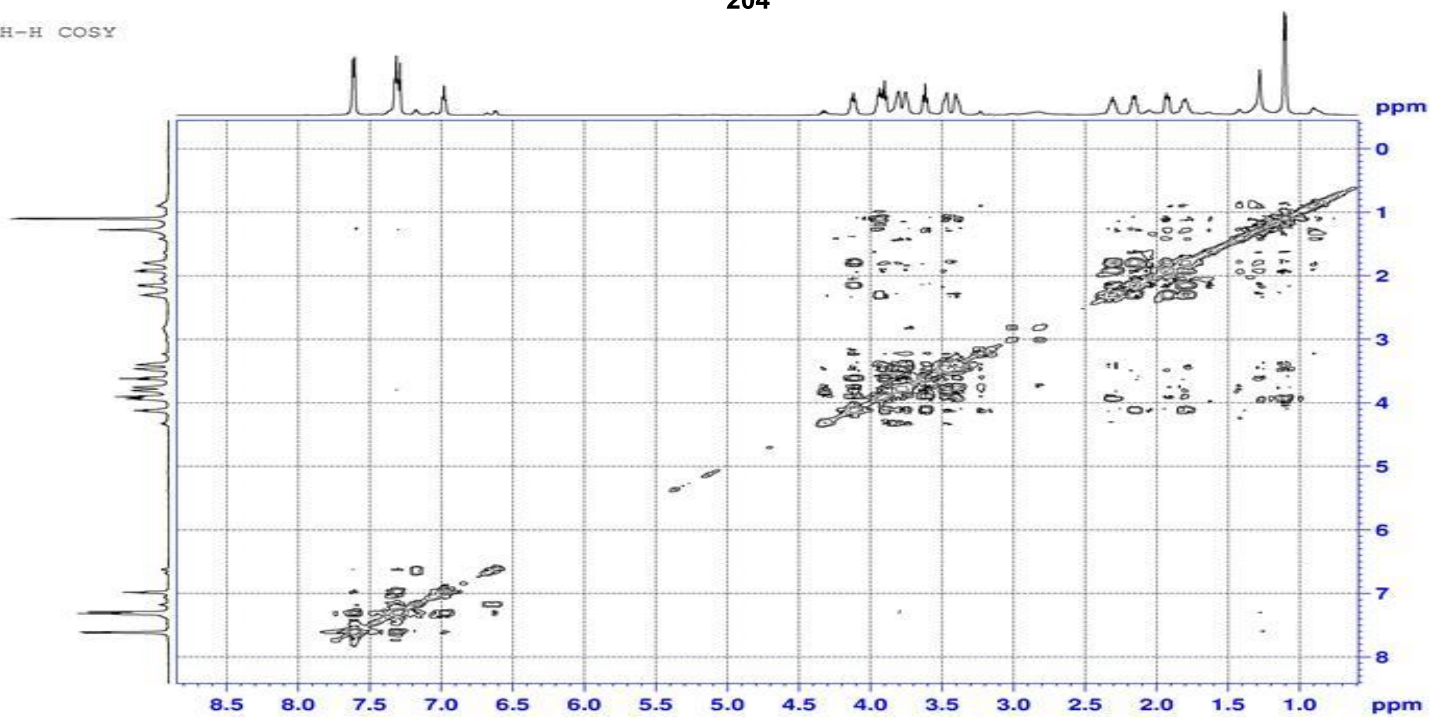
H-H NOESY



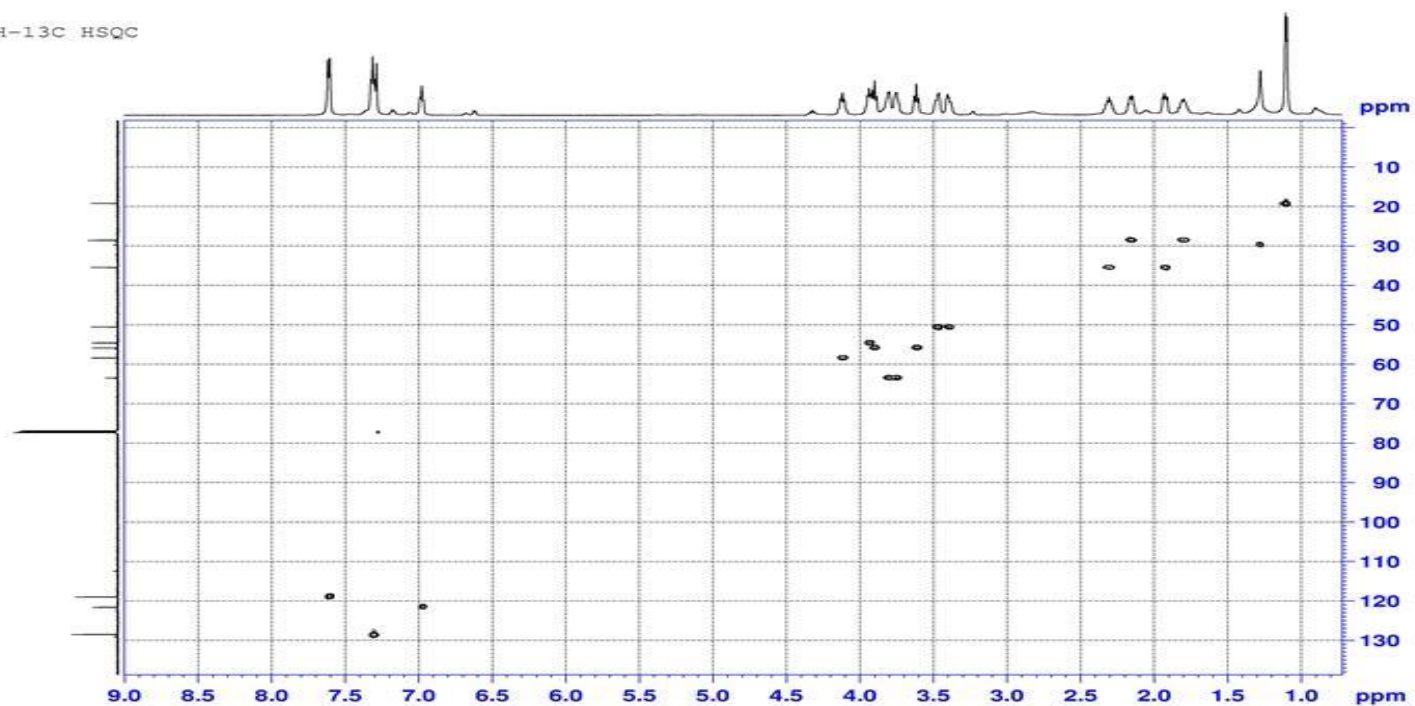


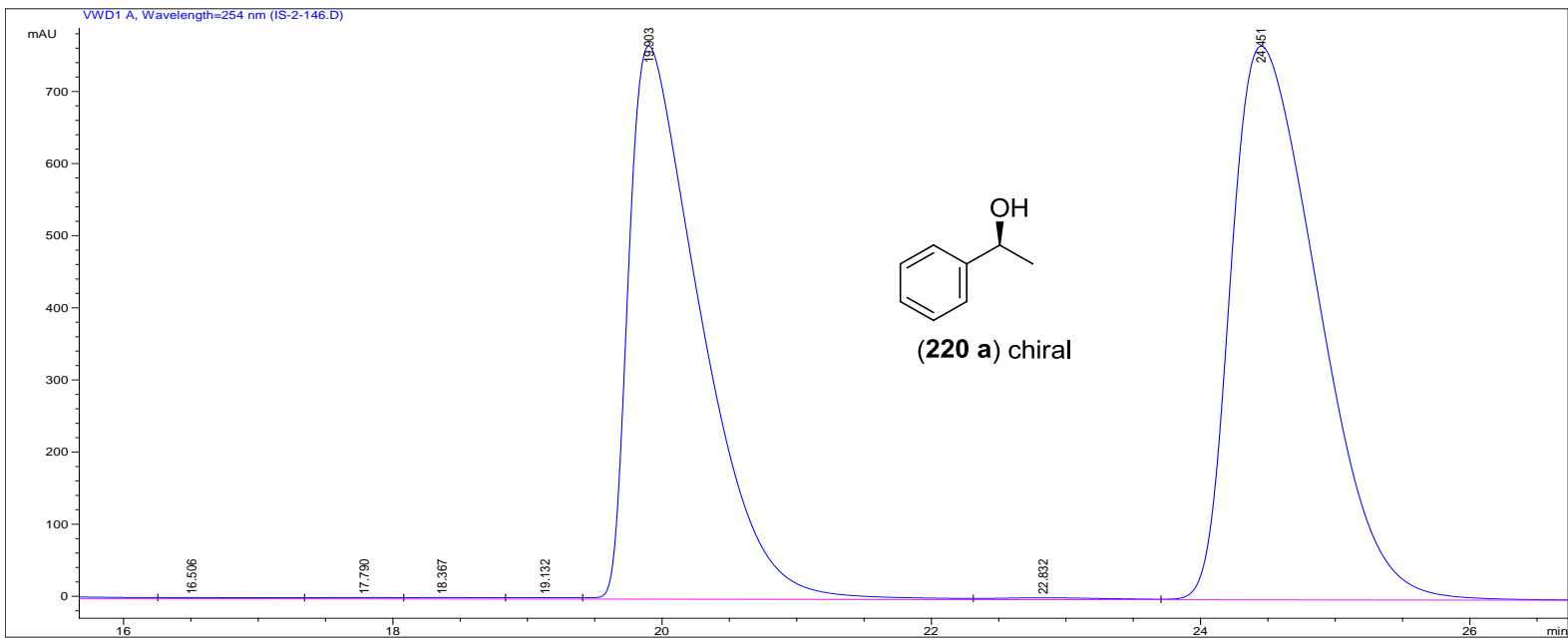
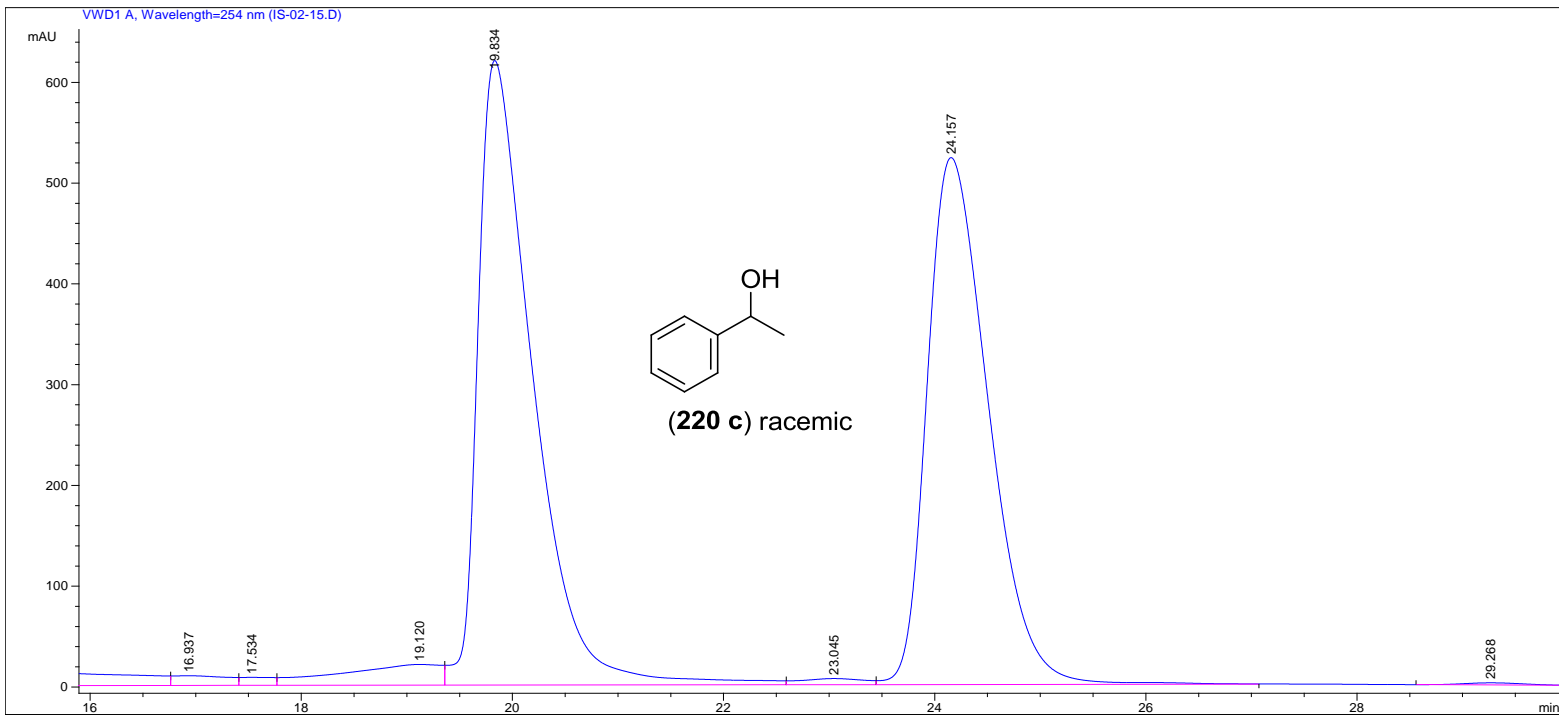
204

H-H COSY

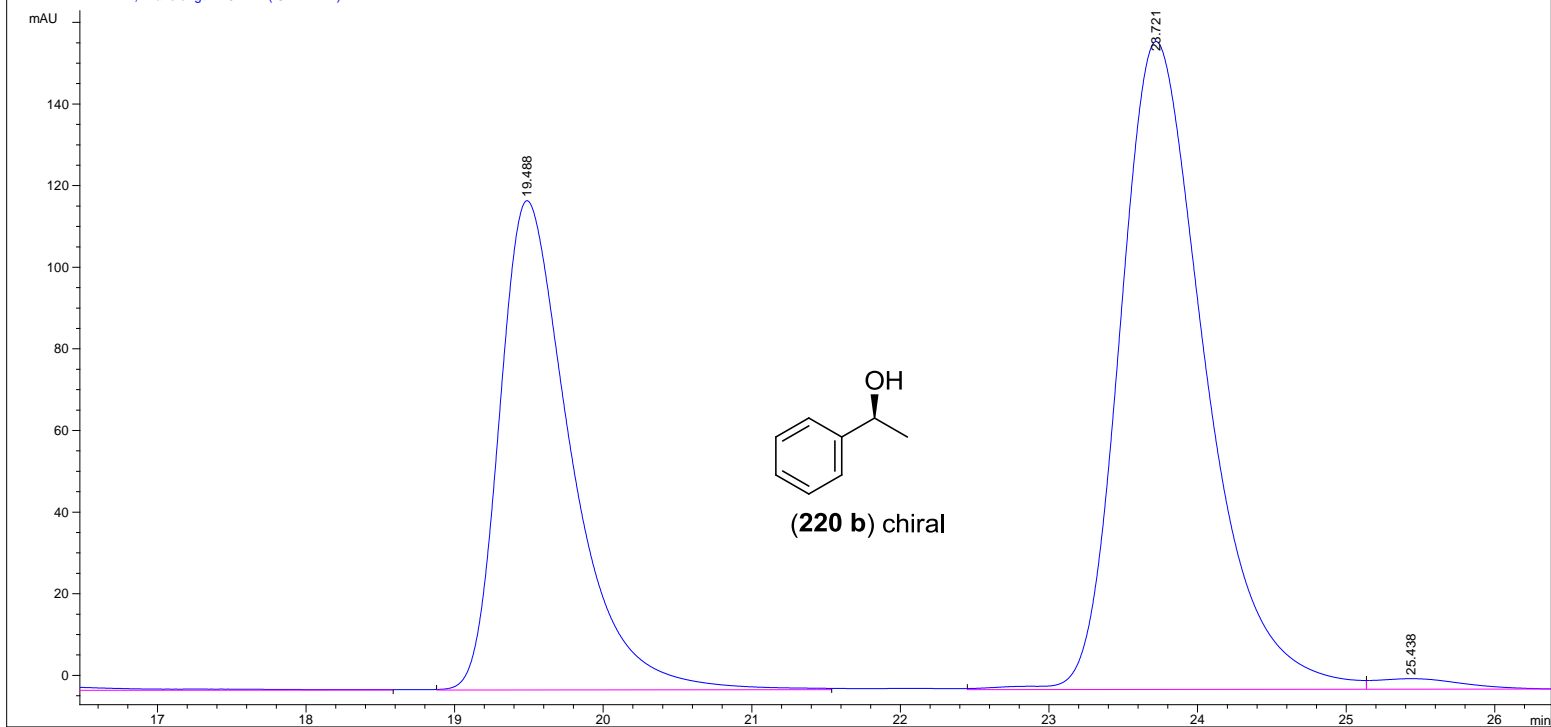


H-13C HSQC





#	RetTime	Type	Area mAU	Height	Width	Area %
18	19.90253	VV	28356.77	766.5344	0.548071	43.4743
20	24.45084	VBA	34494.92	767.499	0.716545	52.8848



#	RetTime	Type	Area mAU	Height	Width	Area %
9	19.48777	BB	4009.38	119.875	0.506687	28.9892
10	23.72072	BV	6339.506	158.7509	0.605669	45.8369